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Review Article

Immuno-oncology of differentiated thyroid cancer

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ABSTRACT

Thyroid cancer has become an epidemic due to easy availability of ultrasound of the neck, and in some countries, routine health checkup ultrasound of neck is routinely done and mandatory. Thyroid cancer detected incidentally and less than 1 cm may warrant only observation, whereas some cancers such as anaplastic thyroid cancer requires urgent intervention. Advances in the field of oncology have been revolutionized by the extensive study of tumor microenvironment (TME). The introduction of immune check point inhibitors resulted in a major shift in the understanding of differentiated thyroid cancer. Inflammation related to thyroid cancer involves various molecular patterns of cytokines and chemokines. They form the major targets for novel immunotherapies. Addition of discovery of newer tumor markers has significantly contributed to cancer management. Tumor immune escape is an important mechanism of oncogenesis. Innate immunity forms the major defense of the body to tumor cells. Polymorphonuclear leucocytes, macrophages, and lymphocytes form the defense that target tumor cells. The aim of this review is to comprehensively discuss the dynamic immune system, various oncogenic pathways and novel tumor antigens like cancer testis sperm associated antigen (SPAG9).

Keywords: Immune cells, Immune checkpoints, Tumor microenvironment, Differentiated thyroid cancer, Immune evasion

INTRODUCTION

Thyroid cancers have a wide spectrum ranging from indolent microcarcinomas to well differentiated macro carcinomas as well as advanced disease. The major subtypes of differentiated thyroid cancer (DTC) include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma. Differentiated cancers of the thyroid account for 97% of the cases which have increased in the recent years. The increase in incidence is due to increased detection of indolent cancers as well as 1.5-5-fold increase in aggressive cancer.[1] The association of thyroid cancer with inflammation has major implications in the mechanisms of tumor environment infiltration by immune cells. Tumor immune escape forms another important pathway for tumor growth. It consists of three phases: Elimination, equilibrium, and escape.[2] The poor prognosis associated with chronic lymphocytic thyroiditis forms the basis of immune system interaction with tumor cells.[3] Tumor markers have been a lacuna in the field of thyroid cancer treatment. Recently, SPAG9 has been identified with a role in theranostics of thyroid cancers. Janus kinase and MAP kinase pathways form the tumor resistance mechanisms to these cancers.[4] "Immune surveillance" and "tumor immunoediting" proposed by Burnet, Thomas and Dunn *et al.* support the perspective of tumor immune hypothesis. "Seed and soil theory" given by Paget further strengthened the idea of TME and its role in metastases.[5] "Camouflage and sabotage" are the two methods of downregulation major histocompatibility complexes (MHC) and modification

of the host immune system by tumor cells.[6] This review is an honest attempt to delve into the details of immune hypothesis in thyroid oncology and their significance in diagnostic and therapeutic advances.

IMMUNOLOGICAL BASICS AND THEIR ASSOCIATION OF THYROID CANCER

Major transformation in the field of thyroid cancer management has been immune checkpoint blockade (ICB) therapy introduced in other cancers, now tried in thyroid malignancies. Immune checkpoints are important in downregulating the immune response. Cytotoxic T Lymphocyte Antigen 4 was one of the first immune checkpoints identified for therapy, which has progressed over the years with PD1, PDL1, and PDL2. Upregulation of PD1 will result in malignancy with activation and T cell dysfunction. PDL1 is responsible for self-immunological tolerance in normal tissue. T regulatory cells are known locally invasive and advanced DTC. B regulatory cells on the other hand suppress immune response with their marker CD19.[7]

Response to immune checkpoint inhibitors have been studied widely. Expression of PDL1 on the tumor cells or leucocytes is considered a biomarker for clinical response, though not specific. Loss of MHC1 and beta-2 microglobulin have been postulated to be the reasons for resistance to ICB therapy. Increased levels of myeloid derived suppressor cells (MDSC) and tumor heterogeneity are also known for poor prognosis. Subsets of MDSC's- polymorphonuclear, monocytic, and early types all markers of DTC. Cyclooxygenases (COXs), which are part of the arachidonic acid cascade, are known to play a role in some tumors. They are known to result in progression of tumors and angiogenesis due to the association of COX and vascular endothelial growth factor. COX2 results in proliferation of follicular cells as part of oncogenesis of undifferentiated and medullary thyroid cancers more than DTC.[7,8]

The two parts of the immune system involved in tumor response are innate and adaptive immunity. Innate immunity includes recognition and phagocytosis, while adaptive immunity is the memory of the tumor response. Toll-like receptors (TLR) with TLR2 and TLR4 are part of both innate and adaptive immunity responsible for the release of cytokines and chemokines. TLR3 is overexpressed in the inflammatory conditions of the thyroid like Hashimoto's thyroiditis. Dendritic cells form the markers of follicular variant of PTC. Mast cells are highly concentrated in thyroid cancer cells – mainly the DTC. Adaptive immunity consists of T cell, B cell regulation, tumor infiltrating lymphocytes, and T helper cells. Lower levels of CD8+T cells and decreased ratio of CD8/Foxp3+T cells in PTC's are aggressive tumors with a larger tumor diameter. Decreased concentration of CD8+T cells would mean greater tumor growth and increased invasive nature. Interferon gamma is another important cytokine secreted by T cells as part of adaptive immunity, which plays a major role in blocking tumor growth. All three types of interferons promote tumor cell apoptosis and subsequent tumor cell death. IFN-γ contributes to immunosuppression by three processes- inhibiting cell proliferation, apoptosis, and induction of macrophages to destroy tumor cells. Natural killer cell infiltration is known to be higher in early stages of DTC than advanced stages and is more pronounced in PTC than the multinodular goitres.[2,9,10]

Malignancies of the thyroid are known to be low risk due to the low mutation burden in them. Mutation burden is known to indicate tumor aggressiveness and response in the field of oncology. Higher the antigenicity of the tumor, higher the T cell response. New targets in the domain of advanced thyroid cancers include BRAF V600E and H/K/NRAS. Gene fusions like RET and other pathways such as PI3K, AKT, and MTOR are other identified targets. Other important antigens described are thyroid specific proteins such as thyroglobulin and thyroid peroxidase. Thyroglobulin expression is responsible for local and advanced DTC. Dedifferentiated cancers on the other hand have complete loss of thyroid peroxidase. The new favorite in the field of immunological therapy is the ICB in advanced thyroid cancer.[11-14]

In advanced malignancies rather than DTC's, higher levels of PDL1 are expressed on the tumor cells which bind to PD1 resulting in exhaustion of T cells. Rationale of combining a TKI with ICB would be to increase tumor immunity and prolong survival in patients. TKI's or BRAF inhibitors would induce tumor cell death and also release tumor cell antigens, thus enhancing immunity. Advanced thyroid cancers, including RAIR DTC – (radioactive iodine resistant), have been treated with Pembrolizumab for 2 years. A partial response of 50% reduction in tumor size was noted within 4–5 months of treatment. A median progression free survival of 7 months was documented in an ongoing trial.[13] Likewise, oncogenic BRAF signaling is known to have reduced tumor antigenicity and treated with MEK inhibitor (Binimetinib) and Nivolumab. Numerous ongoing trials have investigated various drugs in the treatment of RAIR DTC, as mentioned in Table 1.[15-19] ASCO 2017 published the usage of Sorafenib and Lenvatinib in advanced DTC.[20] Another new area of the study includes myeloid suppression by inhibition of colony-stimulating factor (CSF1) an promote differentiation of macrophages. Tumor vaccine strategies such as oncolytic viruses and anti-carcinomembryonic antigen by varying T-cell specific tumor response are another area of progress. Moonshot project 2020 has been an initiative in the cancer vaccine arena. Enhancement of tumor related T cell function is the principle of tumor vaccine. They have been studied in many trials with medullary carcinoma thyroid and advanced

Table 1: Immune Checkpoint Blockers therapy.

Thyroid cancer	Therapy	Trial
DTC	Pembrolizumab (anti-PD1)	KEYNOTE-028 15
DTC	Nivolumab (anti -PD1) and Ipilimumab (anti Cytotoxic T Lymphocyte Antigen 4)	16
DTC and PDTC	Pembrolizumab and Lenvatinib	17
DTC and PDTC	Cabozatinib, Nivolumab and Ipilimumab	18
BRAFV600E mutated cancer	Nivolumab, Encorafenib and Binimetinib	19

thyroid cancers more than DTC. The idea is to boost anti-cancer immunity with the transfer of active immune cells in a vaccine. Vaccines are developed with the help of next generation sequencing, stimulating the host immunity to fight against tumor antigens. Dendritic cell vaccines are more effective since they have the ability to modulate the immune system easily.[21] Pre-clinical studies include chimeric antigenic receptor (CAR) T-cell therapies and their targets-intercellular adhesion molecule in the treatment of advanced DTC and anaplastic thyroid carcinoma. CART cell therapy has shown higher survival but with an associated immunosuppression and other side effects.[7,22]

These newer drugs come with their own drawbacks. Most common adverse events include hypertension, diarrhea, fever, rash, and liver enzyme abnormalities. These are usually managed with supportive treatment, dose reduction, and symptomatic treatment.[1-13]

Genomic analysis has classified various tumors based on the various components of tumor microenvironment (TME). Each of these are given an "immunoscore." PTC falls under the category of "inflammatory" tumors. This is supported by the associated of DTC with thyroiditis and its good prognosis. These immunoscores have also been correlated with degrees of differentiation and certain genetic components. Some enrichment scores with dendritic cells, mast cells in PTC's have been associated with poor differentiation score and BRAFV600E mutation. Mast cells are immature precursor cells derived from the bone marrow. They are present in peripheral blood circulation system and form functional mast cells once they enter peripheral tissues. Tumor associated macrophages (TAM) form another important component of TME which cause remodeling of the extracellular matrix, blocks immune response, promotes angiogenesis, and invasion. They consist of two subsets – M1 and M2 and M2 associated with more aggressive thyroid cancer. The mechanism of binding of TAM to chemokine receptors (CXCR1/2) and secretion of chemokines (CXC8) is responsible for metastasis in most cancer cells resulting in poor prognosis. Higher levels of chemokines, such as CCR2, CCR20, CXCL8, and CXCL12, are noted in RET/PTC and BRAF-positive PTC. CXCL12 particularly is associated with angiogenesis and metastasis. Hence, CXCL12 has been used as a diagnostic marker in these thyroid cancers. Neutrophils form an integral part of inflammatory phases, body's defence against external pathogens, and cancer initiation. The neutrophil-to-lymphocyte ratio–(NLR) in the peripheral circulation has been a standard index of systemic inflammation. It has been linked to tumor development. Increased NLR cannot differentiate benign from malignant nodules are associated with an increased tumor size and higher chance of recurrence. The ratio is also known to be higher in DTC than the general population with no relation to survival.[18]

SPAG9 protein and its immunogenicity are another novel area of interest in thyroid cancers. There is evidence of tumor cell growth reduction by altering MAPK pathways, thus a significant part of thyroid oncogenesis. SPAG9 mRNA and the protein were expressed in 78% of patients with PTC as published by Garg *et al*. There was a good antibody response noted in all early thyroid cancer patients, reiterating their role in diagnostics. Silencing SPAG9 expression using small interfering RNA has a potential role as a therapeutic target in thyroid cancers by reducing cellular growth and proliferation. This protein is thus regarded as an early marker in thyroid tumor particularly early DTC.[5]

The role of cancer associated fibroblasts (CAF) in thyroid cancers is still introductory and is known to be part of tumor initiation, inflammation, metastasis, and immune surveillance. The association between CAF related proteins and clinicopathological factors in PTC was evaluated and found to have a shorter overall survival. It was also known to be a risk factor for lymph node metastasis, along with tumor size.[22]

Newer investigational methods like mass spectrometry have identified newer targets for therapy including TGF-beta-induced protein igH3 (TGFBI) in follicular cancers. PTC on the other hand was found to have higher levels of tenascin, decorin, and AGR2.[23]

CONCLUSION

This review article is an insight into the more recent immunological mechanisms and targets in DTC. Further, strategies to stop the immune escape and promote immune defense in the field of thyroid cancer would be required to be developed. There has been remarkable progress in the study of TME, the role of thyroid inflammatory cells, innate, and adaptive immunity. There is enough evidence about oncogenes and their transcriptional regulation of PI3K/AKT/MTOR pathways. Furthermore, immune responses

through chemokines, cytokines – the protumorigenic role of these entities require research. All this has led to extensive preclinical and clinical trials in anticancer immunotherapy which includes ICB, antibodies against PD1, PDL1, and tumor vaccines. Advances in immunotherapy could make treatments of RAIR and advanced DTC feasible adding long-term survival to their advantage.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. French JD. Immunotherapy for advanced thyroid cancers rationale, current advances and future strategies. Nat Rev Endocrinol 2020;16:629-41.
2. Chand G, Rizwan A. Immunological oncogenic factors in differentiated thyroid cancer. J Endocrinol 2020;4:000150.
3. Liotti F, Prevete N, Vecchio G, Melillo RM. Recent advances in understanding immune phenotypes of thyroid carcinomas: Prognostication and emerging therapies. F1000Res 2019;8:F1000.
4. Ward LS. Immune response in thyroid cancer: Widening the boundaries. Scientifica 2014;2014:125450.
5. Garg M, Kanojia D, Suri S, Gupta S, Gupta A, Suri A. Sperm-associated antigen 9: A novel diagnostic marker for thyroid cancer. J Clin Endocrinol Metab 2009;94:4613-8.
6. Naoum GE, Morkos M, Kim B, Arafat W. Novel targeted therapies and immunotherapy for advanced thyroid cancers. Mol Cancer 2018;17:51.
7. Yin H, Tang Y, Guo Y, Wen S. Immune microenvironment of thyroid cancer. J Cancer 2020;11:4884-96.
8. Xie Z, Li X, He Y, Wu S, Wang S, Sun J, *et al*. Immune cell confrontation in the papillary thyroid carcinoma microenvironment. Front Endocrinol 2020;11:570604.
9. Na KJ, Choi H. Immune landscape of papillary thyroid cancer and immunotherapeutic implications. Endocr Relat Cancer 2018;25:523-31.
10. Ji B, Liu Y, Zhang P, Wang Y, Wang G. COX-2 expression and tumor angiogenesis in thyroid carcinoma patients among northeast Chinese population-result of a single-center study. Int J Med Sci 2012;9:237-42.
11. Takahashi S, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Inagaki L, *et al*. A Phase II study of the safety and efficacy of lenvatinib in patients with advanced thyroid cancer. Future Oncol 2019;15:717-26.
12. Varricchi G, Loffredo S, Marone G, Modestino L, Fallahi P, Ferrari SM, *et al*. The immune landscape of thyroid cancer in the context of immune checkpoint inhibition. Int J Mol Sci 2019;20:3934.
13. Juhasz F, Boros P, Szegedi G, Balazs G, Suranyi P, Kraszits E, *et al*. Immunogenetics and immunologic studies of differentiated thyroid cancer. Cancer 1989;63:1318-26.
14. Ferrari SM, Fallahi P, Galdiero MR, Ruffilli I, Elia G, Ragusa F, *et al*. Immune and inflammatory cells in thyroid cancer microenvironment. Int J Mol Sci 2019;20:4413.
15. Mehnert JM, Varga A, Brose MS, Aggarwal RR, Lin CC, Prawira A, *et al*. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. BMC Cancer 2019;19:196.
16. US National Library of Medicine; 2019. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03246958. [Last accessed on 2020 Dec 15].
17. US National Library of Medicine; 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02973997. [Last accessed on 2020 Dec 15].
18. US National Library of Medicine; 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03914300. [Last accessed on 2020 Dec 15].
19. US National Library of Medicine; 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04061980. [Last accessed on 2020 Dec 15].
20. Mehnert AM, Varga A, Brose M, Aggarwal RR, Lin CC, Prawira A, *et al*. Pembrolizumab for advanced papillary or follicular thyroid cancer: Preliminary results from the phase 1b KEYNOTE-028 study. J Clin Oncol 2016;34:6091.
21. Wang X. Cancer moonshot 2020: A new march of clinical and translational medicine. Clin Transl Med 2016;5:11.
22. Cho JG, Byeon HK, Oh KH, Baek SK, Kwon SY, Jung KY, *et al*. Clinicopathological significance of cancer-associated fibroblasts in papillary thyroid carcinoma: A predictive marker of cervical lymph node metastasis. Eur Arch Otorhinolaryngol 2018;275:2355-61.
23. Martinez-Aguilar J, Clifton-Bligh R, Molloy MP. Proteomics of thyroid tumours provides new insights into their molecular composition and changes associated with malignancy. Sci Rep 2016;6:23660.

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