The Use of Immunotherapy in Papillary Thyroid Cancer

Pok, A., Pearson, A.N.

Introduction

Cancer is the uncontrollable growth of cells that arise from genetic mutations. The immune system is a collection of cells, tissues, and organs working to identify and eliminate infections and diseases. The immune system prevents cancerous cells from proliferating by activating adaptive immune cells with properties such as cytotoxicity, ability to bind with antigens, anti-tumor immunity, and immunity memory. Cancer avoids these mechanisms by downregulating its MHC self-thumbprint to be unrecognizable to the immune cells, blocking costimulation of immune T cells, and upregulating immune checkpoints to turn T cells off. Immunotherapy is a treatment that helps the immune system fight cancer. It is an attractive option to overcome cancer evasion for patients who wish to avoid surgery or chemotherapy. This review will explore one of the many types of cancer, Papillary Thyroid Cancer, and how recent advancements in immunotherapy are being developed to treat it.

Overview of PTC

Representing the majority of all thyroid cancers, Papillary Thyroid Cancer (PTC) is the 8th most common cancer among Americans, making it an important health concern as incidences of PTC begin to rise. PTC's origins are undetermined but are likely contributed by radiation exposure, prior thyroid issues, excessive iodine intake, or genetic inheritance (Weeks 2018). PTC is prevalent in middle-aged white females, who are 2-3 times more likely to develop papillary thyroid cancer than men. High increases occurring in individuals around 60-79 years old suggest that hormonal changes caused by menopause can be associated with female risk of developing PTC (Enewold 2009). Patients often report symptoms of neck mass, dyspnea, and hoarseness of voice. Common mutations include changes in the *BRAF* gene that creates a constantly activated *BRAF* oncogene and causes cells to proliferate; a mutation in the RAS gene that responds similarly to the *BRAF* oncogene; and developed mutations in the PTC oncogene commonly caused by radiation in youth (American Cancer Society 2024). People who develop PTC often have a 5-year relative survival rate of over 99% in localized and regional stages, and 74% in distant stages (American Cancer Society 2024).

PTC Immunotherapy

Papillary thyroid cancer (PTC) evades the immune system by downregulating NK cells, T cells, and inhibiting immune checkpoints. NK cells are immune cells that distinguish "self vs non-self" in the tumor microenvironment (TME). Tumor cells secrete immunosuppressive factors, reducing the activation receptors on NK cells, as well as reducing MHC I molecule expression to block tumor antigen presentation. Regulatory T cells (Tregs) show high levels in PTC tumors, inhibiting anti-tumor immunity through cAMP and exosome pathways. Unlike healthy thyroid tissue, PTC inhibits immune checkpoints including LAG3, PD-1, and IDO1, associated with the prevention of immune cell-mediated damage to healthy thyroid tissue (Xun 2024). Common immunotherapies for PTC include chemotherapy and iodine radiotherapy for early stages. Radioiodine therapy (RAI) can be ingested through a pill, shot, or drink, and collects in the thyroid cells after exposure to the bloodstream (American Cancer Society). RAI is

used to destroy remaining thyroid tissue and target cancer that may have spread to other organs from the existing PTC. Risks include radiation exposure and increased risk of a second cancer developing. Patients with advanced PTC, however, are more likely to be resistant to radiation and chemotherapy treatments and require alternatives to these now ineffective options. Adoptive cell therapies or immune checkpoint inhibitors (ICIs) are good substitutes. ICIs are antibodies that target specific immune checkpoints, and prevent PTC tumor cells from interacting with immune cells by blocking checkpoint proteins from binding to corresponding proteins, and allowing the T cells to recognize and kill cancer cells (National Cancer Institute 2022). Studies in mouse carcinoma revealed that the combination of ICIs with BRAF inhibitors significantly reduced tumor volume. Despite this newfound knowledge, ICIs depend on the patient's immune status before being used because their efficiency is limited by personalized gut microorganisms. Sometimes after the use of ICIs, occurrences of side effects such as rashes and other symptoms may appear (Xun 2024). Although there are no current FDA-approved immunotherapies for PTC, extensive research is being done on specific genes that may limit PTC proliferation. A Science Direct study was conducted to explore the previously unknown effects of *TGFBR3* as a possible tumor in PTC, as it tends to be in other cancers. Researchers found that the overexpression of *TGFBR3* was linked to the inhibition of proliferation, migration, and invasion of PTC cells. The gene was also found to inhibit the PI3K-AKT pathway, where alterations in this pathway can lead to tumorigenesis. Results showed that samples in the high *TGFBR3* expression group had fewer M0 macrophages and regulatory T cells (involved in immune regulation) and a significant increase in CD8+ T cells (helpful for killing cancer cells) and CD4+ memory resting T cells (help maintain long-term immune response). These results portray *TGFBR3* overexpression as a potential candidate for immunotherapy in PTC. (Zhang 2024).

PTC is the 5th most common cancer among women, creating a significant impact on public health (Wu 2025). Early-stage PTC usually has a low mortality rate but becomes more dangerous when metastases develop or PTC is immune to immunotherapies. Circular RNAs (circRNAs) are a "unique class of single-stranded transcripts that are formed through a process called back-splicing, resulting in a covalently closed loop structure," which functions to regulate many biological processes (Wu 2025). They can serve as sponges for microRNAs (miRNAs), scaffolding proteins, decoys, transcriptional regulators, and templates for protein translation and can modify tumor growth pathways to either inhibit or promote PTC. Primary approaches to get rid of PTC include surgical removal and radiotherapy, but in cases where the disease is advanced/immune to radiotherapy, there are not many solutions. An increasing number of circRNAs, including circNEIL3 and circARID1A, also play critical roles in regulating interactions between proteins and ribonucleoprotein complexes because they can bind to and sequester specific proteins, directing them to particular subcellular locations, which in turn influences tumor development.

Innovation

A study conducted by Hanrong Zhang and other collaborators explored the *TGFBR3* gene, which is known as a tumor suppressor in other cancers but had an unknown role in PTC. Their article discusses the effects of the *TGFBR3* gene and how its overexpression in PTC cells can decrease the tumor's proliferation. The study was conducted to explore the previously

unknown effects of *TGFBR3* as a possible tumor in PTC, as it tends to be in other cancers. Their lab procedure included purchasing PTC tumors from the Cell Bank of Type Culture Collection of the Chinese Academy of Sciences from 10 different patients and scraping those cells to conduct a wound healing assay. Western blotting was used to detect the protein expression level of *TGFBR3* in those cells. Researchers found that the overexpression of *TGFBR3* was linked to the inhibition, proliferation, migration, and invasion of cancerous PTC cells by binding to TGFβ1-3 and inhibiting the TGF-β pathway. The gene was also found to inhibit the PI3K-AKT pathway, where alterations in this pathway can lead to tumorigenesis, which is the process by which normal cells become cancerous. Results showed that samples in the high *TGFBR3* expression group had fewer M0 macrophages and regulatory T cells (involved in immune regulation) and a significant increase in CD8+ T cells (helpful for killing cancer cells) and CD4+ memory resting T cells (help maintain long-term immune response). These results portray *TGFBR3* overexpression as a potential candidate for immunotherapy in PTC.

A clinical trial (NCT03246958) conducted by the Dana-Farber Cancer Institute researches two investigative immunotherapies called nivolumab and ipilimumab as combination treatments for thyroid cancers. This phase II clinical trial aims to test the safety and effectiveness of this combination therapy in thyroid cancer, where it has yet to be FDA-approved for non-metastatic tumors. Patients enrolled must meet the inclusion criteria of being at least 18 years old, having metastatic, RAI refractory, or differentiated thyroid cancer (including PTC), and having normal organ function. The exclusion criteria are people with autoimmune diseases, patients who have had chemotherapy or radiation therapy, or conditions requiring treatment from immunosuppressive medication. This trial helps address previous limitations by utilizing dual checkpoint inhibition to enhance immune response in PTC. Future innovation will focus on combination therapies to optimize the role of immunotherapy in PTC suppression.

Conclusion

Papillary Thyroid Cancer is the most prevalent thyroid cancer that is characterized by mutations often from radiation exposure. PTC is not very responsive to immunotherapies, and there have yet to be any FDA-approved treatments. PTC expresses resistant mechanisms such as downregulating NK cells, T cells, and inhibiting immune checkpoints. Immunotherapies like ICIs and other adoptive cell therapies have been explored to treat PTC. While ICIs in combination with BRAF inhibitors have demonstrated promising reduction of tumors, this method's effectiveness is limited by the individual patients' immune status and limitations by their gut microbiome. Researchers are currently studying the roles of genes like *TGFBR3* in preventing PTC cell proliferation, as well as circRNAs for negatively influencing tumor development. The main obstacles include a lack of FDA-approved immunotherapies, resistance to currently researched treatments, and the necessity for a better understanding of the relationship between circRNAs and tumors. Immunotherapy can have an enormous impact on reducing PTC proliferation and even lead to future FDA-approved treatments, especially for patients resistant to ICI combination. By taking advantage of the current enigma of *TGFBR3* and circRNAs, scientists may be able to develop effective immunotherapies that decrease dependency on surgery and radioiodine treatments in the near future.

References

1. American Cancer Society. (2023, February 28). Radioactive Iodine (Radioiodine) Therapy for Thyroid Cancer. Www.cancer.org. https://www.cancer.org/cancer/types/thyroid-cancer/treating/radioactive-iodine.html
2. Survival Rates for Thyroid Cancer. (n.d.). Www.cancer.org. https://www.cancer.org/cancer/types/thyroid-cancer/detection-diagnosis-staging/survival-rates.html
3. Zheng Xun, Sun Ruonan, & Wei Tao. (2024). Immune microenvironment in papillary thyroid carcinoma: roles of immune cells and checkpoints in disease progression and therapeutic implications. Frontiers in Immunology, 15. https://doi.org/10.3389/fimmu.2024.1438235
4. National Cancer Institute. (2022, April 7). Immune Checkpoint Inhibitors. National Cancer Institute; Cancer.gov. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors
5. Weeks, K. S., Kahl, A. R., Lynch, C. F., & Charlton, M. E. (2018). Racial/ethnic differences in thyroid cancer incidence in the United States, 2007-2014. Cancer, 124(7), 1483–1491. https://doi.org/10.1002/cncr.31229
6. Enewold, L., Zhu, K., Ron, E., Marrogi, A. J., Stojadinovic, A., Peoples, G. E., & Devesa, S. S. (2009). Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 18(3), 784–791. https://doi.org/10.1158/1055-9965.EPI-08-0960
7. Gang Wu, Chao Ding, Chen-Lei Shi, Xiao-Cong Zhang, Guo-Rong Lei, Shuang Wang, Hua-Dong Qin, Tie-Feng Shi, Circular RNA 14580 promotes papillary thyroid cancer progression by interacting with CTSW/fibrosis signaling pathway, International Journal of Biological Macromolecules, Volume 286, January 2025
8. Hanrong Zhang, & BackgroundTransforming growth factor beta receptor III (TGFBR3) has been shown to play a tumor-suppressive role in a variety of cancers. However. (2024, November 21). TGFBR3 inhibits progression of papillary thyroid cancer by inhibiting the PI3K/akt pathway and EMT. Endocrine Connections. https://www.sciencedirect.com/org/science/article/pii/S204936142400114X#fig5
9. NCT03246958