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THYROID CANCER: MOLECULAR, GENETIC, AND CLINICAL ALTERATIONS

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Abstract
Thyroid cancer is a heterogeneous malignancy characterized by distinct molecular and genetic alterations that influence tumor initiation, progression, and clinical behavior. Advances in genomic and transcriptomic profiling have identified recurrent mutations and rearrangements, including BRAF V600E, RAS, RET/PTC, and TP53, which play crucial roles in tumor proliferation, differentiation, and metastatic potential. These molecular changes are closely associated with histopathological subtypes, guiding risk stratification, prognostic assessment, and therapeutic decision-making. Clinical manifestations of thyroid cancer, such as tumor size, lymph node involvement, and aggressiveness, often correlate with underlying genetic profiles. Comprehensive understanding of molecular and genetic mechanisms has facilitated the development of targeted therapies, including kinase inhibitors and precision medicine approaches, improving patient outcomes. This review summarizes current knowledge on molecular, genetic, and clinical alterations in thyroid cancer and highlights their implications for diagnosis, prognostication, and individualized treatment strategies.

Keywords: Thyroid cancer; molecular alterations; genetic mutations; BRAF; RAS; RET/PTC; TP53; targeted therapy; precision medicine; clinical features.

Introduction

Thyroid cancer is the most common endocrine malignancy, with increasing incidence worldwide over the past decades. It encompasses a heterogeneous

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group of tumors, including papillary, follicular, medullary, and anaplastic subtypes, each exhibiting distinct molecular, genetic, and clinical characteristics. Papillary thyroid carcinoma (PTC) represents the majority of cases and is frequently associated with BRAF V600E mutations and RET/PTC rearrangements, whereas follicular thyroid carcinoma (FTC) often harbors RAS mutations. Medullary thyroid carcinoma (MTC) is linked to germline or somatic RET mutations, and anaplastic thyroid carcinoma (ATC) demonstrates complex genomic alterations, including TP53 mutations, reflecting its highly aggressive nature.

The pathogenesis of thyroid cancer is driven by the interplay of genetic mutations, epigenetic modifications, and aberrant signaling pathways, such as MAPK and PI3K-AKT, which regulate cell proliferation, differentiation, and survival. These molecular alterations not only determine tumor behavior but also influence clinical presentation, including tumor size, invasiveness, lymph node metastasis, and recurrence risk. Understanding these mechanisms has become crucial for risk stratification, prognostic assessment, and the implementation of targeted therapies in clinical practice.

Despite advances in detection and treatment, a subset of thyroid cancers exhibits aggressive features and poor response to conventional therapies, underscoring the need for precise molecular characterization and personalized management strategies. Integration of molecular diagnostics into routine clinical workflows offers opportunities for early detection, optimized therapeutic interventions, and improved patient outcomes.

Molecular and Genetic Alterations in Thyroid Cancer

Thyroid cancer development and progression are driven by a spectrum of molecular and genetic alterations that vary among histological subtypes. Papillary thyroid carcinoma (PTC), the most common form, is frequently associated with BRAF V600E mutations, which constitutively activate the MAPK signaling pathway, promoting cell proliferation, dedifferentiation, and tumor progression. RET/PTC rearrangements, resulting from chromosomal inversions or translocations, also activate MAPK signaling and are implicated in PTC pathogenesis, particularly in radiation-associated cases.

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Follicular thyroid carcinoma (FTC) is often characterized by mutations in RAS genes (HRAS, KRAS, NRAS) and PAX8-PPARG rearrangements, which influence PI3K-AKT and MAPK pathways, enhancing tumor cell growth and survival. Medullary thyroid carcinoma (MTC) arises from parafollicular C cells and is strongly linked to germline or somatic RET mutations, which drive oncogenic signaling and determine hereditary versus sporadic forms of the disease.

Anaplastic thyroid carcinoma (ATC), a highly aggressive subtype, demonstrates a complex mutational landscape, including TP53 inactivation, TERT promoter mutations, and alterations in PI3K-AKT and Wnt/β-catenin pathways. These genetic changes confer rapid tumor growth, invasion, and resistance to conventional therapies. Epigenetic modifications, including DNA methylation, histone modification, and microRNA dysregulation, further contribute to thyroid tumor heterogeneity and aggressiveness.

Recent advances in next-generation sequencing and genomic profiling have allowed precise identification of driver mutations and actionable genetic alterations. This molecular characterization not only enhances diagnostic accuracy but also informs prognostication and facilitates the development of targeted therapies, including kinase inhibitors and precision medicine approaches, tailored to specific genetic profiles. Understanding these molecular and genetic mechanisms is therefore critical for optimizing clinical management and improving outcomes in thyroid cancer patients.

Clinical Manifestations and Correlation with Molecular Alterations

Thyroid cancer exhibits a wide spectrum of clinical presentations, which are often influenced by underlying molecular and genetic alterations. Papillary thyroid carcinoma (PTC), typically associated with BRAF V600E mutations and RET/PTC rearrangements, usually presents as a slow-growing thyroid nodule, often asymptomatic, but may demonstrate local lymph node metastases even in early stages. BRAF V600E mutations in particular correlate with aggressive histopathological features, including extrathyroidal extension, multifocality, and higher recurrence risk.

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Follicular thyroid carcinoma (FTC), frequently harboring RAS mutations or PAX8-PPARG rearrangements, often presents as a solitary thyroid nodule and is more prone to hematogenous spread, especially to lungs and bones, reflecting its distinct molecular profile. Medullary thyroid carcinoma (MTC), driven by RET mutations, may present with thyroid nodules, cervical lymphadenopathy, or systemic symptoms such as diarrhea and flushing due to hormone secretion. Hereditary forms of MTC, such as MEN2 syndromes, demonstrate early-onset disease with multifocal involvement, underlining the importance of genetic screening.

Anaplastic thyroid carcinoma (ATC), associated with TP53 and TERT promoter mutations, presents aggressively with rapidly enlarging neck mass, airway compromise, and early distant metastasis. The aggressive clinical behavior of ATC mirrors its complex genomic landscape, characterized by multiple oncogenic drivers and genomic instability.

Overall, correlating molecular and genetic alterations with clinical features allows for improved risk stratification, personalized treatment planning, and prognostic assessment. Integration of molecular diagnostics into routine clinical practice enhances early detection of aggressive disease and guides the selection of targeted therapies, ultimately improving patient outcomes.

Targeted Therapies and Precision Medicine Approaches

Advances in the understanding of molecular and genetic alterations in thyroid cancer have facilitated the development of targeted therapies, enabling precision medicine approaches tailored to specific oncogenic drivers. For papillary thyroid carcinoma (PTC) harboring BRAF V600E mutations, selective BRAF inhibitors, alone or in combination with MEK inhibitors, have demonstrated efficacy in patients with progressive or radioiodine-refractory disease, resulting in tumor regression and improved clinical outcomes. RET inhibitors, such as selpercatinib and pralsetinib, have shown significant therapeutic benefit in patients with RET-mutant medullary thyroid carcinoma (MTC) and RET fusion-positive PTC, highlighting the clinical importance of molecular profiling.

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For RAS-mutated follicular thyroid carcinoma (FTC), clinical trials are exploring MEK and PI3K pathway inhibitors, although effective targeted options remain limited compared to BRAF or RET-driven cancers. Multikinase inhibitors, including lenvatinib and sorafenib, have been approved for advanced, progressive, or radioiodine-refractory differentiated thyroid cancers, providing a broader therapeutic strategy by simultaneously targeting multiple signaling pathways. In anaplastic thyroid carcinoma (ATC), characterized by TP53, TERT promoter, and other high-risk mutations, combination therapies involving kinase inhibitors, immune checkpoint inhibitors, and conventional modalities are under investigation to improve survival in this highly aggressive subtype.

Integration of comprehensive genomic profiling into clinical workflows enables identification of actionable mutations, guiding therapy selection and monitoring treatment response. Precision medicine strategies not only improve the efficacy of therapeutic interventions but also minimize toxicity, optimize patient outcomes, and pave the way for individualized management in thyroid cancer. Continuous research into novel molecular targets and combination therapies holds promise for expanding the therapeutic arsenal and addressing resistance mechanisms in refractory thyroid malignancies.

Conclusion

Thyroid cancer is a genetically and clinically heterogeneous disease, driven by distinct molecular alterations that dictate tumor behavior, aggressiveness, and response to therapy. Understanding the spectrum of genetic mutations, including BRAF, RAS, RET/PTC, and TP53, and their correlation with clinical manifestations is essential for accurate diagnosis, prognostication, and risk stratification. The integration of molecular profiling into clinical practice enables the implementation of targeted therapies and precision medicine approaches, improving outcomes in patients with differentiated, medullary, and anaplastic thyroid cancers. Continuous research into novel molecular pathways, therapeutic targets, and combination strategies is crucial for addressing refractory disease and further personalizing thyroid cancer management. Overall, a comprehensive understanding of molecular, genetic, and clinical alterations provides the foundation for optimized, patient-centered care in thyroid oncology.

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