

Revisión



GENOMIC INSTABILITY AS MECHANISM IN THYROID CANCER DEVELOPMENT

Jesuino de Oliveira Andrade L.¹; Correia Matos de G.²; Santana de P.R.¹; Vinhaes Bittencourt A.M.³; De Mattos Salles O.J.⁴; De Oliveira L.M.¹

¹Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil.

²José Silveira Foundation, Salvador, Bahia, Brazil.

³School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil.

⁴Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil.

INFORMACIÓN DEL ARTÍCULO

Historia del artículo:

Recibido: 11/09/2025

Revisión: 27/11/2025

Aceptado: 14/12/2025

Palabras clave:

Cáncer de tiroides

Tumorigénesis

Genómica

RESUMEN

El cáncer de tiroides emerge en un contexto de múltiples factores de riesgo que reflejan el alto potencial proliferativo inherente a las células foliculares tiroideas. Entre estos factores, la inestabilidad genómica se destaca como un mecanismo fundamental que impulsa la tumorigénesis tiroidea. Esta revisión tiene como finalidad esclarecer el papel de la inestabilidad genómica en la patogénesis del cáncer de tiroides, examinando las alteraciones moleculares y los oncogenes clave involucrados en la iniciación y progresión tumoral. Se realizó un análisis de los estudios citogenéticos y moleculares actuales para sintetizar el conocimiento acerca de las mutaciones genéticas y aberraciones cromosómicas asociadas con lesiones tiroideas benignas y malignas. La inestabilidad genómica contribuye significativamente al desarrollo tumoral tiroideo mediante la acumulación de alteraciones genéticas que afectan vías de señalización cruciales. Estas alteraciones influyen en el fenotipo tumoral y en el comportamiento a lo largo de las diferentes fases de progresión. Además, los avances en tecnologías diagnósticas han optimizado la identificación de nuevas variantes génicas y la caracterización de perfiles moleculares vinculados a fenotipos tumorales específicos de tiroides. Comprender los mecanismos moleculares subyacentes a la inestabilidad genómica proporciona insights críticos para la carcinogénesis tiroidea y resalta posibles dianas para el perfeccionamiento diagnóstico y terapéutico. Los principales oncogenes involucrados en este proceso constituyen prometedores focos de investigación futura.

ABSTRACT

Keywords:

Thyroid cancer
Tumorigenesis
Genomic

Thyroid cancer arises in the context of numerous risk factors that reflect the intrinsically high proliferative potential of thyroid follicular cells. Among these factors, genomic instability has emerged as a fundamental mechanism driving thyroid tumorigenesis. This review aims to elucidate the role of genomic instability in the pathogenesis of thyroid cancer, examining the molecular alterations and key oncogenes implicated in tumor initiation and progression. An analysis of current cytogenetic and molecular studies was conducted to synthesize the knowledge surrounding genetic mutations and chromosomal aberrations associated with both benign and malignant thyroid lesions. Genomic instability contributes significantly to thyroid tumor development through the accumulation of genetic alterations affecting crucial signaling pathways. These alterations influence tumor phenotype and behavior across different stages of progression. Moreover, advances in diagnostic technologies have improved the identification of novel gene variants and the characterization of molecular profiles linked to specific thyroid tumor phenotypes. Understanding the molecular underpinnings of genomic instability offers critical insights into thyroid carcinogenesis and highlights potential targets for diagnostic and therapeutic refinement. The principal oncogenes driving this process represent promising focal points for future research.

INTRODUCTION

Thyroid cancer, while relatively uncommon, ranks among the most prevalent malignancies of the endocrine system, accounting for approximately 1% of all new cancer diagnoses worldwide. In the United States, an estimated 44,020 new cases of thyroid cancer are projected for 2025, with an associated mortality of approximately 2,200 deaths per year attributed primarily to differentiated thyroid carcinoma (DTC). In Brazil, the incidence is estimated at approximately 7.6 cases per 100,000 population per year, with recent projections indicating several thousand new cases diagnosed annually, and mortality rates remaining relatively low but stable.^{1,2,3}

Genomic instability is recognized as a critical contributor to the multi-step process of tumorigenesis in thyroid cancer. Cytogenetic analyses have elucidated the central role of genomic instability in the initiation and progression of thyroid malignancies. The oncogenic transformation process involves the sequential activation of oncogenes alongside the inactivation of tumor suppressor genes, resulting in cumulative genetic alterations within a clonal lineage of cells and a consequent inability to regulate mitogenic signaling effectively.⁴

Genomic instability orchestrates thyroid tumorigenesis through chromosomal aberrations, microsatellite alterations, elevated mutational burden, and oncogenic structural rearrangements, collectively disrupting cellular homeostasis and enabling malignant transformation.⁵

At the cellular level, tumorigenesis in thyroid tissue is predominantly characterized by chromosomal alterations. While normal thyroid follicular cells maintain diploid chromosomal content to coordinate regulated growth and division both *in vivo* and *in vitro*, neoplastic cells frequently exhibit chromosomal aberrations, including aneuploidy, which disrupt normal cellular homeostasis. Although diploid chromosomes in normal cells may sustain damage, the cellular machinery typically initiates apoptotic pathways to eliminate damaged cells. However, cancer cells often evade apoptosis, leading to intensified chromosomal disorganization and instability.⁶

During early tumorigenesis, neoplastic thyroid cells acquire enhanced genomic instability that endows them with capabilities absent in normal cells. This progressive accumulation of genetic aberrations destabilizes key mechanisms governing the cell cycle, promoting uncontrolled proliferation and loss of growth regulation, particularly through mutations in genes regulating cell cycle checkpoints. Thyroid tumorigenesis thus represents a complex and progressive accumulation of genetic alterations driven by underlying genomic instability.^{7,8}

This article aims to elucidate the mechanistic role of genomic instability in driving thyroid tumorigenesis, exploring its impact on cell cycle dysregulation and the accumulation of pro-oncogenic chromosomal aberrations.

METHODOLOGICAL APPROACH

This narrative review synthesizes current knowledge on genomic instability mechanisms in thyroid carcinogenesis through a comprehensive examination of peer-reviewed literature spanning the period from 1990 to 2025. Searches were conducted across multiple databases including PubMed/MEDLINE, Scopus, and Web of Science. The search strategy employed combinations of Medical Subject Headings (MeSH) terms and keywords including "thyroid cancer," "genomic instability," "chromosomal aberrations," "RET/PTC rearrangements," "BRAF mutations," "tumor suppressor genes," and "thyroid tumorigenesis." Priority was given to original research articles, systematic reviews, and meta-analyses published within the last decade, supplemented by seminal earlier works that established foundational concepts in the field.

TUMORIGENESIS MECHANISM

The cell cycle comprises four sequential phases (G1, S, G2, and M) orchestrating cellular proliferation through tightly regulated molecular checkpoints governed by cyclin-dependent kinases (Cdks) and cyclins (Figure 1).^{9,10} Surveillance checkpoints preserve genomic integrity by monitoring DNA replication fidelity and initiating repair mechanisms before progression. The G1 restriction point represents a critical regulatory node determining commitment to division or quiescence. Neoplastic transformation requires multiple cumulative genetic alterations, typically five to six successive mutations, alongside evasion of cell cycle checkpoints.¹¹ Cells initially respond to genomic damage

through cycle arrest, enabling DNA repair, or when damage proves irreparable, apoptosis eliminates affected cells.¹² Should these mechanisms fail, immune surveillance constitutes a critical defense. If neoplastic cells overcome these barriers, they clonally expand, with progressive aggressiveness depending on additional genetic alterations conferring proliferative and survival advantages.¹³

In thyroid tumorigenesis, cell cycle dysregulation plays a central pathogenic role. Aberrant Cdk5 activity facilitates ubiquitin-mediated degradation of p21, promoting uncontrolled proliferation and malignant transformation.¹⁴ Overexpression of pituitary tumor-transforming gene 1 enhances G2/M progression, driving proliferation, migration, and apoptosis resistance.¹⁵ Non-coding RNAs modulate cell cycle regulators and epithelial-mesenchymal transition, contributing to tumor progression and metastatic potential.¹⁶ Tumor expansion necessitates angiogenesis, orchestrated by vascular endothelial growth factor activation, enabling neoplastic cells to breach tissue barriers and sustain progression.¹⁷ The tumor microenvironment critically influences metastatic dissemination through stromal interactions, determining organ-specific patterns.¹⁸ Tumorigenesis thus encompasses dysregulation of genes encoding cell division proteins: oncogenes promote proliferation, whereas tumor suppressor genes enforce checkpoints and apoptosis, with neoplastic transformation requiring cumulative genomic alterations that overcome tumor-suppressive mechanisms, enabling clonal expansion, angiogenesis-dependent progression, and microenvironment-mediated metastatic dissemination (Figure 2).

Figure 1. Eukaryotic Cell Cycle: Phase Transitions and Molecular Events.

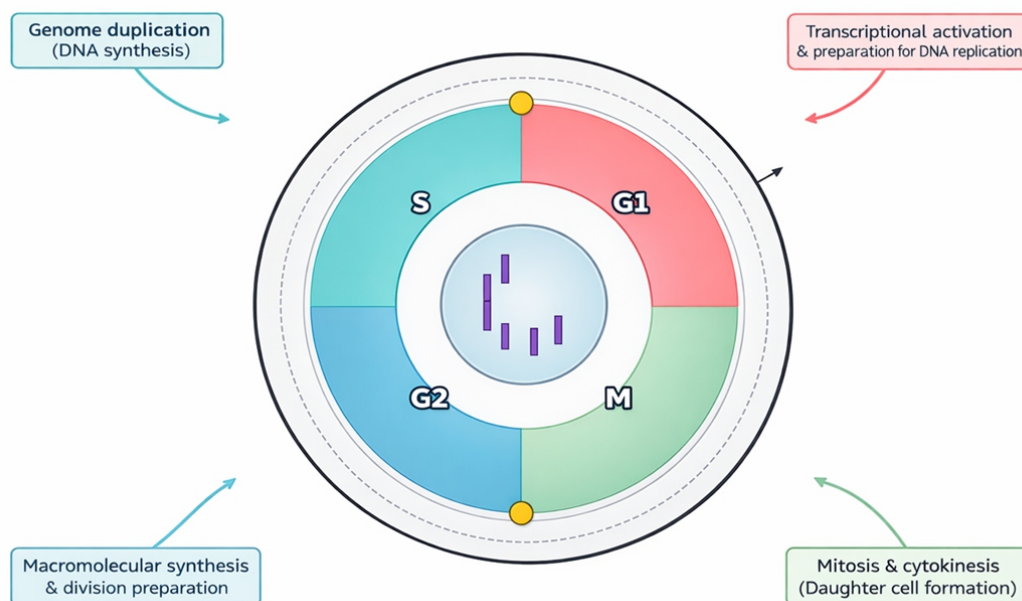
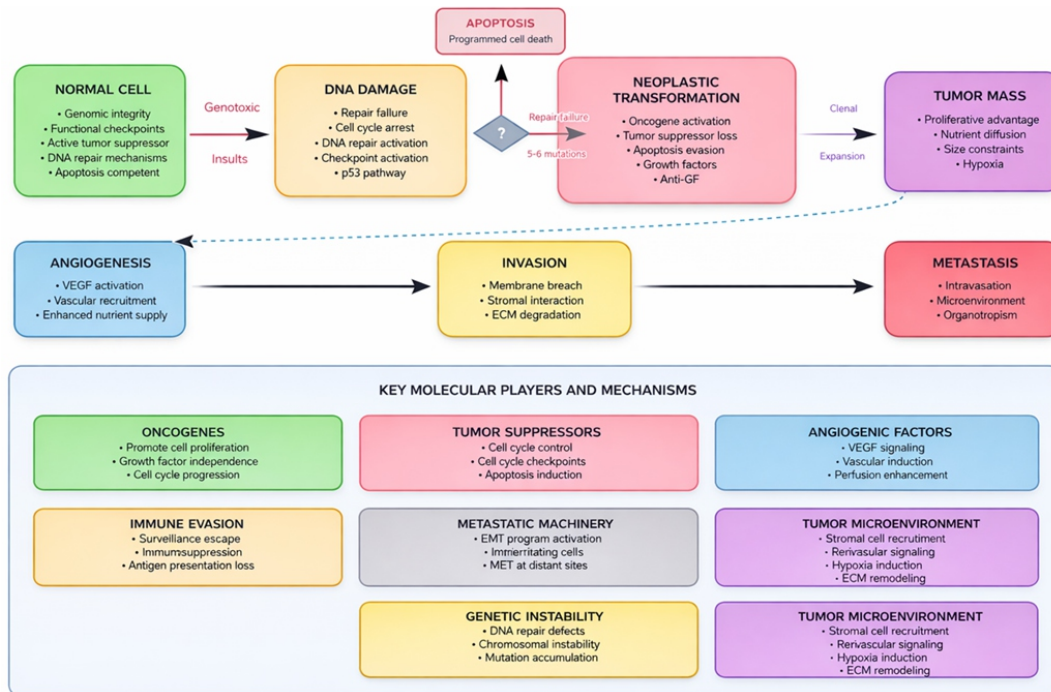


Figure 2. Molecular Mechanisms of Neoplastic Transformation and Tumor Progression



THYROID CARCINOGENESIS

Thyroid carcinogenesis represents a multifactorial process shaped by genetic predispositions, environmental exposures, and hormonal influences. Global incidence has risen over recent decades, particularly among individuals over 40 years, with approximately 5–10% of DTC cases exhibiting familial clustering through autosomal dominant inheritance with incomplete penetrance.¹⁹ Hereditary syndromes including multiple endocrine neoplasia type 2, PTEN hamartoma tumor syndrome, familial adenomatous polyposis, and Carney complex underscore germline mutations as oncogenic drivers (Figure 3).²⁰

Ionizing radiation remains the most potent environmental carcinogen directly linked to genomic instability in thyroid neoplasms.²¹ Historical cohorts from atomic bomb survivors and Chernobyl populations provide unequivocal evidence of radiation-induced carcinogenesis, particularly in children.²² Ionizing radiation induces DNA double-strand breaks that, when misrepaired, generate chromosomal rearrangements, point mutations, and persistent genomic instability. The tumor suppressor protein p53 arrests the cell cycle to facilitate repair or initiates apoptosis; however, thyroid cells surviving radiation exposure accumulate genomic alterations driving malignant transformation.²³ Post-Chernobyl studies revealed high frequencies of proto-oncogene RET/ Papillary Thyroid Carcinoma (RET/PTC) rearrangements and marked genomic instability in pediatric thyroid cancers, with loss of heterozygosity or microsatellite alterations in 31% of cases, predominantly in girls exposed before age 9 who developed more aggressive tumors.²⁴ These findings establish radiation-induced chromosomal rearrangements as a cardinal mechanism

of genomic instability in thyroid tumorigenesis, with spatial proximity of chromosomal loci during DNA damage enabling illegitimate recombination and oncogenic fusion formation.

Additional risk factors modulate cancer susceptibility and histological subtypes but contribute less directly to genomic instability. Dietary iodine intake influences tumor phenotype: iodine deficiency correlates with higher follicular thyroid carcinoma (FTC) prevalence, whereas iodine sufficiency favors papillary thyroid carcinoma (PTC).²⁵ Female predominance (F:M ratio ~3:1) implicates hormonal influences,²⁶ though nodules in men exhibit higher malignancy rates and more aggressive disease.²⁷ Pre-existing benign thyroid conditions frequently precede malignancy, with Hashimoto's thyroiditis paradoxically associated with improved outcomes, potentially reflecting enhanced immune surveillance.²⁸

GENES INVOLVED IN THYROID TUMORIGENESIS

Thyroid tumorigenesis involves complex genetic alterations across multiple oncogenic pathways, with distinct patterns of genomic instability characterizing different histological subtypes. The phenotypic manifestation depends on the type and timing of genomic alterations, encompassing both spontaneous and radiation-induced neoplasms.²⁹ Genetic alterations can be categorized as either genomically "stable" events (point mutations occurring in diploid genomes) or "unstable" events (chromosomal rearrangements, fusions, and copy number alterations reflecting underlying chromosomal instability) (Figure 4).

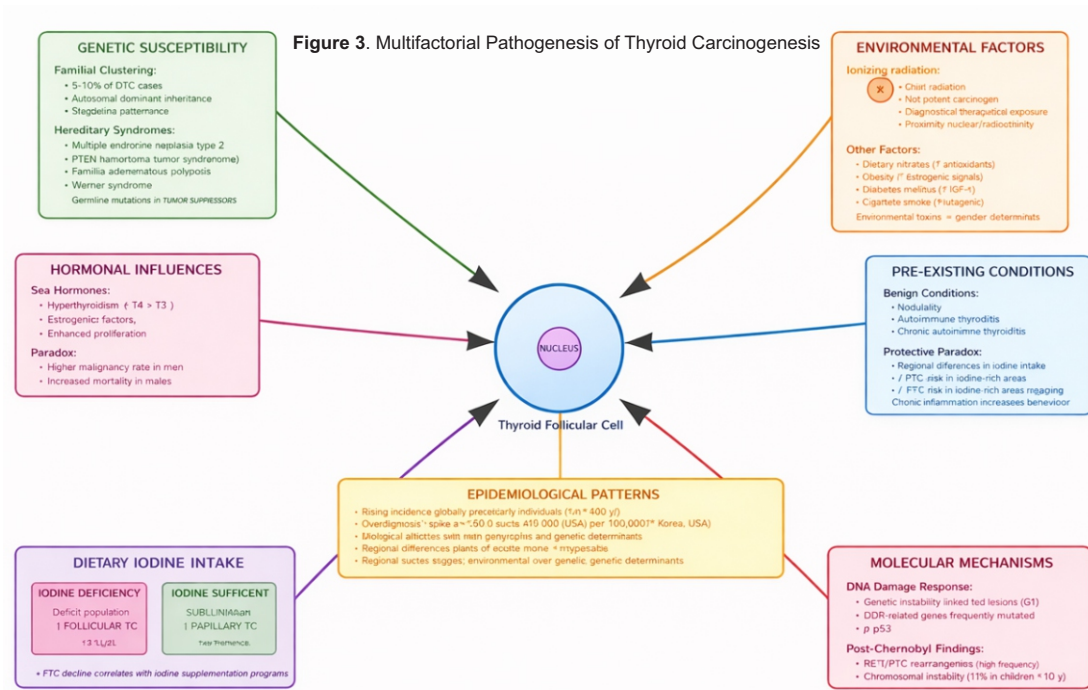
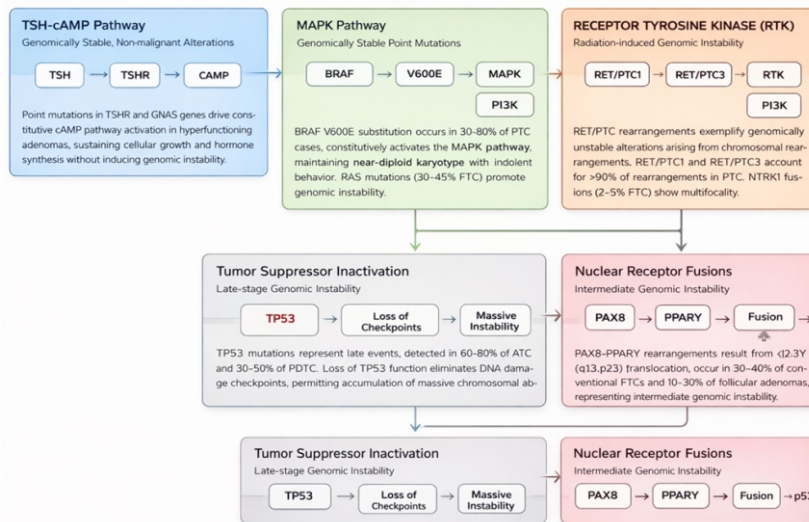


Figure 4. Pathway-organized genetic alterations in thyroid tumorigenesis



TSH-cAMP Pathway: Genomically Stable, Non-malignant Alterations

Point mutations in TSHR and GNAS genes drive constitutive cAMP pathway activation in hyperfunctioning adenomas, sustaining cellular growth and hormone synthesis without inducing genomic instability.³⁰ These mutations predominate in autonomously functioning nodules and toxic adenomas³¹ but do not predispose to malignant transformation, explaining their rarity in thyroid carcinomas. This pathway exemplifies genomically stable alterations that maintain diploid status and lack chromosomal aberrations characteristic of malignant progression.

MAPK Pathway: Genomically Stable Point Mutations

BRAF V600E substitution, a thymine-to-adenine transversion at nucleotide 1796, occurs in 30–80% of PTC cases (commonly

37–48%) and constitutively activates the MAPK pathway.^{42,43,32} Despite high oncogenic potency, BRAF-mutant PTCs typically exhibit genomic stability, maintaining near-diploid karyotypes and demonstrating indolent clinical behavior. BRAF mutations are also detected in ~29% of anaplastic thyroid carcinoma (ATC) cases, often as late events accompanying genomic instability and dedifferentiation.³³ RAS family mutations (H-RAS, K-RAS, N-RAS) represent early events in thyroid carcinogenesis, occurring in 30–45% of FTC and follicular adenomas.³⁴ Unlike BRAF, RAS mutations actively promote genomic instability, facilitating accumulation of subsequent genetic alterations and progression toward malignancy. The incidence in FTC (10.5–56.9%) exceeds that in follicular adenomas (8–48%), highlighting their role in malignant transformation of follicular phenotype neoplasms.³⁵

Receptor Tyrosine Kinase (RTK) Rearrangements: Radiation-induced Genomic Instability

RET/PTC rearrangements exemplify genomically unstable alterations arising from chromosomal rearrangements. RET/PTC1 and RET/PTC3, intrachromosomal inversions involving chromosome 10q, account for >90% of rearrangements in PTC.³⁶ These fusions juxtapose the RET tyrosine kinase domain with partner gene sequences, triggering constitutive receptor dimerization and MAPK/PI3K pathway activation.³⁷

Ionizing radiation facilitates spatial proximity of chromosomal loci during DNA damage, enabling illegitimate recombination and RET/PTC formation.³⁸ Radiation-induced PTC exhibits RET/PTC rearrangements in 29–86% of cases, with RET/PTC3 predominating in aggressive childhood tumors with short latency post-Chernobyl (~70% of cases), whereas RET/PTC1 associates with classical papillary phenotype and later onset.³⁹ RET/PTC3 confers more aggressive tumor biology, reflecting heightened genomic instability.⁴⁰ Germline RET mutations cause MEN2 variants through ligand-independent kinase activation.⁴¹

NTRK1 rearrangements (2–5% of PTC) arise from translocations juxtaposing the kinase domain with partner genes (TPM3, TPR, TFG), generating constitutively active fusion proteins.⁴² Post-Chernobyl studies identified NTRK1 rearrangements in 3.3% of cases, associated with multifocality and aggressiveness, reflecting underlying chromosomal instability.⁴³

Nuclear Receptor Fusions: Intermediate Genomic Instability

PAX8-PPAR γ rearrangements, resulting from t(2;3)(q13;p25) translocation, occur in 30–40% of conventional FTCs and 10–30% of follicular adenomas, challenging diagnostic discrimination.⁴⁴ This fusion dysregulates transcriptional programs governing differentiation and proliferation, representing an intermediate level of genomic instability between point mutations and radiation-induced rearrangements. PAX8-PPAR γ rearrangements are rare (<2%) in Hürthle cell carcinomas.⁴⁵

Tumor Suppressor Inactivation: Late-stage Genomic Instability

TP53 mutations represent late events in thyroid carcinogenesis, predominantly occurring in advanced, genomically unstable tumors. While rare in well-differentiated carcinomas, TP53 alterations are detected in 60–80% of ATC and 30–50% of PTC, serving as molecular hallmarks of dedifferentiation.⁴⁶ TP53 inactivation eliminates critical DNA damage checkpoints, permitting accumulation of chromosomal aberrations and progression to highly unstable, aggressive phenotypes. These alterations associate with loss of iodine avidity, therapeutic resistance, and reduced survival.⁴⁷

Integrated Tumor Suppressor Networks in Thyroid Tumorigenesis

Tumor suppressor gene networks integrate seamlessly with oncogenic drivers outlined in thyroid tumorigenesis, amplifying genomic instability through coordinated pathway disruptions rather than isolated gene effects.⁴⁸ Central to this network, TP53 inactivation, prevalent in 60–80% of anaplastic thyroid carcinomas and 30–50% of poorly differentiated forms, impairs DNA damage responses, enabling unchecked accumulation of mutations in genes like BRAF V600E and RAS isoforms that initiate papillary and follicular neoplasms. Concurrent loss of heterozygosity (LOH) at loci such as 11q13, 9p21 (CDKN2A/p16), 13q14 (RB1), 3p14 (FHIT), and 17p13 (TP53) fosters a cascade of chromosomal aberrations, with FTC exhibiting higher LOH frequency than genomically stable papillary subtypes.⁴⁹

Network-Level Effects and Genomic Instability

These networks exert effects at multiple scales, where TP53 dysfunction synergizes with DNA repair deficiencies to propagate errors during cell cycle checkpoints, promoting aneuploidy and RET/PTC rearrangements particularly in radiation-exposed tissues.⁵⁰ Sodium Iodide Symporter/SLC5A5 downregulation, observed in 15–30% of differentiated thyroid cancers, exemplifies network collapse as MAPK/PI3K-AKT hyperactivation, driven by upstream oncogenes, silences symporter transcription and trafficking, rendering tumors radioiodine-refractory while exacerbating dedifferentiation.⁵¹ Combined alterations, including CDH1 (16q22) LOH and RB1 loss, disrupt epithelial integrity and G1/S transition, yielding multiplicative genomic instability that shifts indolent lesions toward aggressive, metastatic phenotypes.⁵²

Clinical and Mechanistic Implications

This interconnected dysregulation underscores why PTC maintains relative stability despite RET/PTC fusions, contrasting with follicular-derived instability from multi-locus LOH, informing prognostic stratification and redifferentiation therapies targeting pathway restoration.⁵³ Overall, tumor suppressor erosion creates a permissive environment for oncogene cooperation, driving thyroid carcinogenesis progression.⁵⁴

CONCLUDING REMARKS

This analysis elucidates the pivotal role of genetic instability in the pathogenesis of thyroid neoplasms, delineating the complex network of implicated genes. Contemporary diagnostic methodologies are rapidly evolving, focusing on the identification of novel genetic alterations and the comprehensive profiling of tumor-specific molecular signatures. These advancements are directly translating into refined therapeutic strategies. The emergence of targeted gene

therapy, whether through genetic immunization, replacement of defective alleles, or reactivation of silenced tumor suppressor genes such as p53 to induce selective apoptotic pathways in malignant cells, heralds a new era of precision medicine with significantly improved treatment efficacy and patient outcomes.

Conflicts of interest: None declared.

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