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Genomic Instability as Mechanism in Thyroid Cancer Development

Inestabilidad Genómica como Mecanismo en el Desarrollo del Cáncer de Tiroides

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ABSTRACT

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.

Keywords: Thyroid cancer, Tumorigenesis, Genomic.

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 tumorogénesis 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.

Palabras clave: Cáncer de tiroides, Tumorogénesis, Genómica.

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.[4,5]

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]

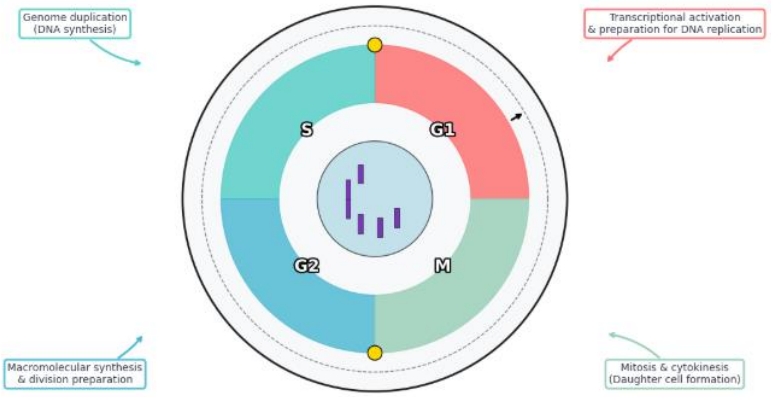
This article aims to elucidate the mechanistic role of genomic instability in driving thyroid tumorigenesis, exploring its impact on cell cycle dysregulation and the accumulation of pro-oncogenic chromosomal aberrations.

TUMORIGENESIS MECHANISM

The cell cycle constitutes a fundamental biological program orchestrating cellular growth and division, composed of four distinct phases: G1, S, G2, and M. During the G1 phase, the cell undertakes the expression of genes critical for protein biosynthesis and prepares for DNA replication. Subsequently, in the S phase, DNA synthesis occurs, resulting in the duplication of the cell's genetic material. Progressing into the G2 phase, the cell resumes biosynthetic activities, synthesizing proteins and increasing in size to ensure readiness for mitosis. Finally, the M phase encompasses mitosis and cytokinesis, whereby the cell divides to produce two genetically identical daughter cells (Figure 1).[9]

This tightly regulated process is governed by complex molecular networks, including cyclin-dependent kinases (Cdks) and their cyclin partners, which modulate phase transitions via phosphorylation events. Cell cycle checkpoints embedded in this sequence act as surveillance systems to preserve genomic integrity by monitoring DNA replication fidelity and repairing damage, when necessary, before progression to subsequent phases. Specifically, the G1 restriction point represents a critical control juncture, determining whether the cell commits to division or enters a quiescent state.[10]

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



Source: Study results

Within the context of thyroid tumorigenesis, aberrations in cell cycle control play a central role. Recent studies have identified that dysregulated Cdk5 activity facilitates the ubiquitin-mediated degradation of p21, a critical Cdk inhibitor, thereby promoting uncontrolled cell proliferation and contributing to malignant transformation in thyroid cancer.[11] Moreover, overexpression of pituitary tumor-transforming gene 1 has been implicated in enhancing G2/M phase progression, promoting proliferation, migration, and apoptosis resistance in thyroid cancer cells, further underscoring the deregulation of cell cycle machinery as a driver of tumor growth.[12] Non-coding RNAs (ncRNAs), including microRNAs and long ncRNAs, have also emerged as modulators influencing cell cycle regulators and epithelial-mesenchymal transition, thereby contributing to tumor progression and metastatic potential in thyroid malignancies.[13]

Disruptions in this regulatory circuitry contribute to uncontrolled proliferation characteristic of neoplastic transformation, underpinning the importance of the cell cycle in tumorigenesis. Comprehensive proteomic and live-cell imaging analyses continue to unravel the dynamic regulatory networks and post-translational modifications that govern precise cell cycle progression and their deregulation in thyroid cancer.

The process by which a normal cell undergoes transformation into a neoplastic cell is gradual and highly complex, involving multiple, successive, and cumulative genetic alterations. This transformation thus constitutes a genetic disease, as daughter cells inherit the genetic modifications present in the progenitor cell that initiated tumorigenesis. Depending on their genetic background and predisposition, cells may respond variably to ongoing oncogenic stimuli. However, sustained tumor formation typically requires multiple insults to the cellular genome, commonly estimated as five to

six successive and additive mutations, alongside the evasion of numerous cell cycle regulatory checkpoints that serve to prevent malignant transformation.[14]

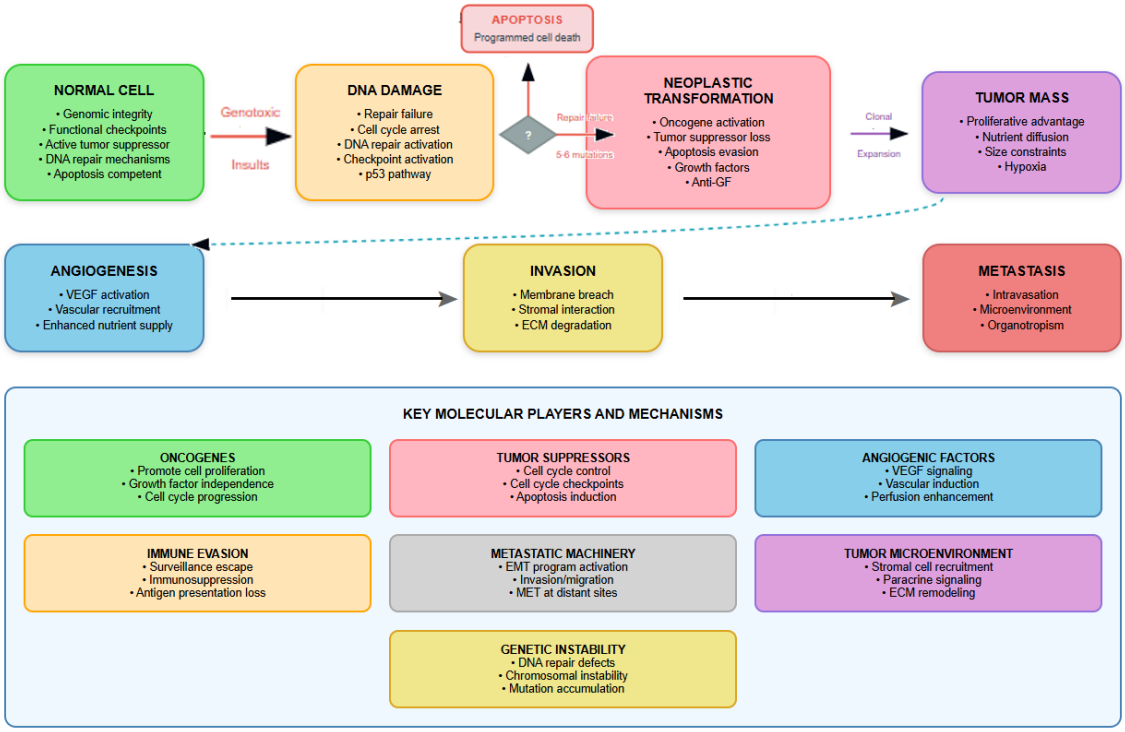
The organism's initial response to aberrant genomic damage involves cell cycle arrest, allowing for DNA repair mechanisms to rectify lesions. When damage is irreparable due to the severity of genotoxic insults, affected cells are directed toward programmed cell death (apoptosis), thereby preventing the perpetuation of potentially oncogenic mutations. Should these tumor-suppressive mechanisms fail, and mutated cells evade apoptosis, the immune system constitutes a critical line of defense by recognizing and eliminating abnormal cells.[15] If neoplastic cells overcome all these barriers, they clonally expand, producing a tumor mass. Progressive tumor aggressiveness and progression are contingent upon the accumulation of additional genetic alterations that confer proliferative and survival advantages to tumor cells.[16]

Initially, this limited population of tumor cells relies on nutrient diffusion from adjacent normal tissues. As the tumor expands, its growth demands an increased supply of oxygen and nutrients, necessitating the induction of angiogenesis, a process orchestrated by the activation of pro-angiogenic genes such as vascular endothelial growth factor. Angiogenesis facilitates tumor invasion by enabling neoplastic cells to breach surrounding tissue barriers, invade through capsules, coalesce with stromal cells, evade immune surveillance, and sustain tumor progression.[17]

The biological context of the tumor microenvironment critically influences metastatic dissemination. Interactions between tumor cells and surrounding stromal and interstitial components determine organ-specific metastatic patterns typical of each cancer type. This indicates that metastatic colonization preferentially occurs in tissues providing suitable paracrine and extracellular signals that foster tumor cell survival and proliferation.[18]

Tumorigenesis encompasses the dysregulation of numerous genes encoding proteins governing cell division. Oncogenes promote tumor progression by stimulating cell proliferation, whereas tumor suppressor genes counteract neoplastic growth by enforcing cell cycle checkpoints and apoptosis (Figure 2).

Figure 2. Molecular Mechanisms of Neoplastic Transformation and Tumor Progression

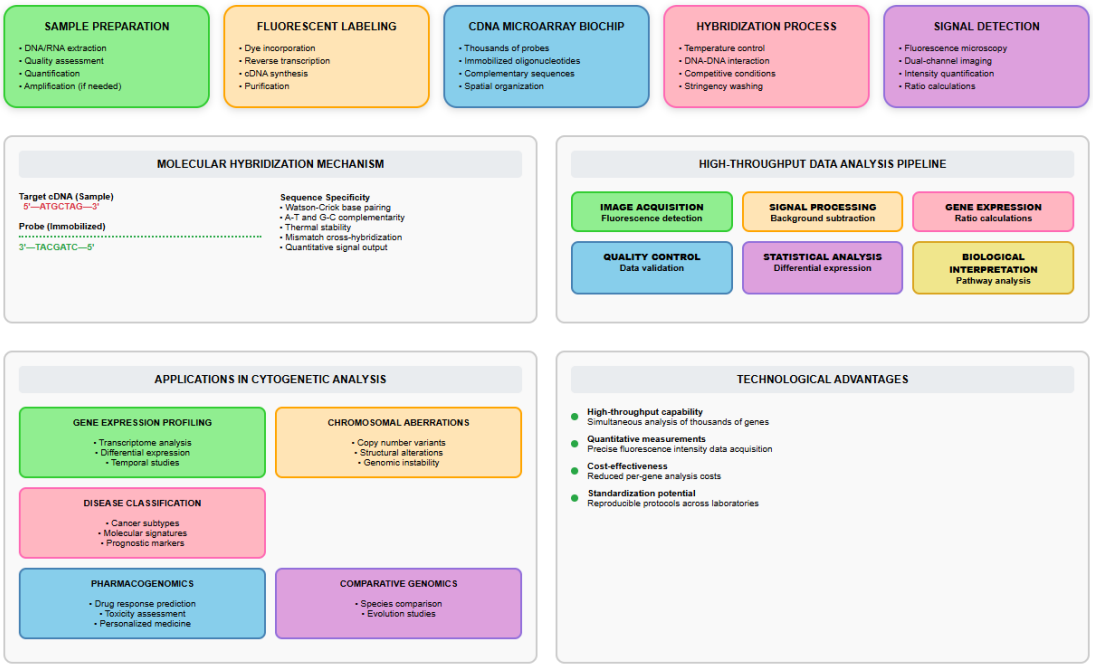


Source: Study results

Thus, neoplastic transformation requires cumulative genomic alterations overcoming tumor-suppressive mechanisms, enabling clonal expansion, angiogenesis-dependent progression, and microenvironment-mediated metastatic dissemination through oncogene activation and tumor suppressor gene inactivation.

The advent of biological microarray technologies, particularly cDNA microarrays, represents a major breakthrough in cytogenetic methodologies, enabling extensive evaluation of genetic alterations across thousands of loci simultaneously.[18] These biochips facilitate the analysis of DNA, RNA, or other biomolecules by leveraging complementary sequence hybridization—whether DNA-DNA or DNA-RNA—to detect and quantify gene expression changes (Figure 3).

Figure 3. Microarray Technology: Principles and Applications in Cytogenetic Analysis



Source: Study results

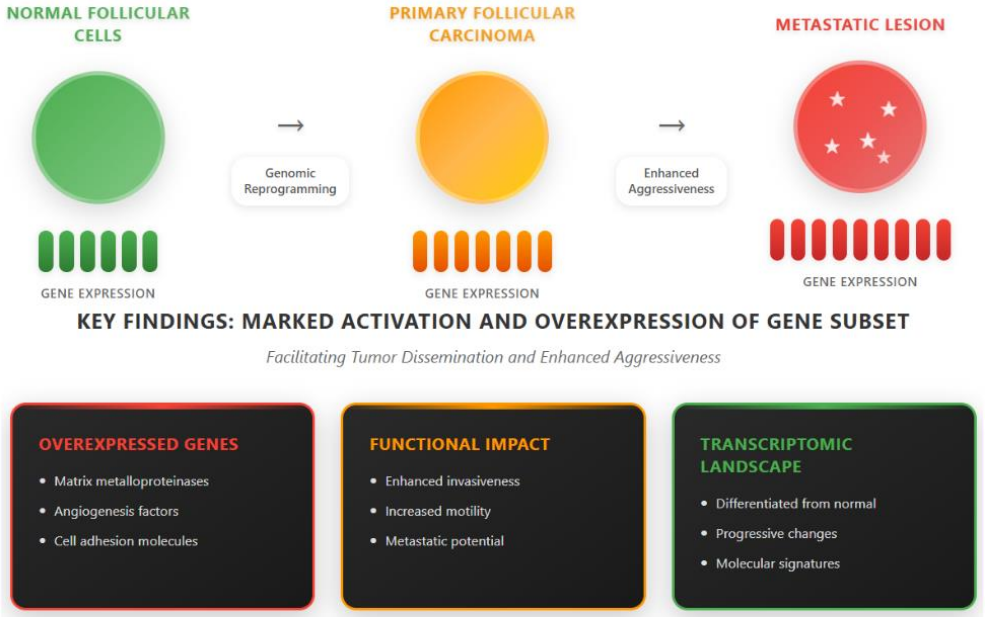
cDNA microarrays consist of glass or polymer slides serving as platforms onto which thousands of known DNA sequences are immobilized in an orderly grid, produced via microarray printing techniques. These sequences can be full-length cDNA, generated from mRNA transcripts, or short oligonucleotides devoid of introns. Typically, each chip surface (~1 cm^2) contains tens of thousands to several hundred thousand discrete spots, each harboring specific nucleic acid probes ranging from approximately 10–20 bases for oligonucleotides to 1,000–2,000 bases for cDNA fragments. This spatial arrangement enables precise hybridization with labeled target sequences based on complementary base pairing, allowing high-throughput, simultaneous interrogation of gene expression profiles.[19]

The fundamental strategy involves probing a panel of oncogenes, apoptosis regulators, cell cycle-related genes, and other proteins implicated in tumor biology to assess differential expression. Genes exhibiting significant overexpression (hyperexpression) or diminished expression (hypoexpression) are identified by measuring hybridization intensities. Those genes demonstrating consistent alterations in expression patterns serve as potential biomarkers for tumor progression and therapeutic targets.[20]

As tumorigenesis advances, neoplastic cells undergo progressive genomic reprogramming, differentiating their transcriptomic landscape from that of normal

counterparts. Comparative analyses of primary follicular thyroid carcinoma (FTC) and their matched metastatic lesions using cDNA microarrays have demonstrated marked activation and overexpression of a subset of genes in metastatic tissues, underscoring their role in facilitating tumor dissemination and aggressiveness (Figure 4).[21]

Figure 4. Genomic Reprogramming in Thyroid Carcinoma Progression

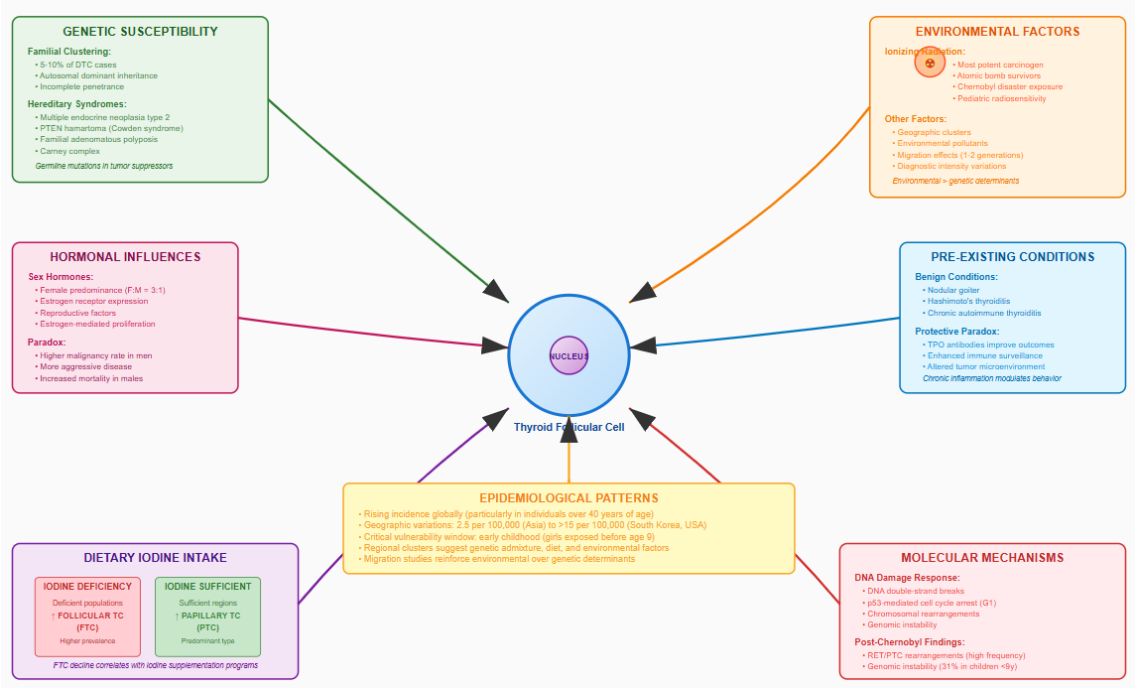


Source: Study results

THYROID CARCINOGENESIS

Thyroid carcinogenesis is a multifactorial, gradual process influenced by genetic predispositions, hormonal regulation, nutritional factors, environmental exposures, and existing glandular conditions. Key elements such as ionizing radiation, iodine deficiency, chronic inflammation, and demographic variables impart molecular alterations that cumulatively shift the cellular environment toward malignancy. Central to this progression are cellular adaptive responses to genomic stress, epigenetic modifications, and dysregulation of signaling pathways. This orchestrated biological process, shaped by both hereditary and external factors, accounts for the heterogeneity observed in thyroid cancer incidence, histology, and clinical behavior across different populations and life stages (Figure 5).

Figure 5. Multifactorial Pathogenesis of Thyroid Carcinogenesis



Source: Study results

Incidence rates have been rising globally over recent decades, particularly among individuals over 40 years of age.[22] Its pathogenesis is multifactorial, involving a complex interplay between genetic susceptibility, environmental exposures, hormonal influences, and pre-existing thyroid pathology.

A significant subset of thyroid carcinomas, particularly DTC, exhibits familial clustering. Approximately 5–10% of DTC cases occur in the context of familial non-medullary thyroid cancer, which demonstrates an autosomal dominant inheritance pattern with incomplete penetrance.[23] Furthermore, several hereditary syndromes are strongly associated with thyroid malignancies, including multiple endocrine neoplasia type 2, PTEN hamartoma tumor syndrome (Cowden syndrome), familial adenomatous polyposis, and Carney complex.[24,25] These syndromes underscore the role of germline mutations in tumor suppressor genes as drivers of thyroid oncogenesis.

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Thyroid cancer frequently arises in the context of pre-existing benign thyroid conditions, including nodular goiter and chronic autoimmune thyroiditis. Interestingly, the presence of thyroid peroxidase antibodies and a history of Hashimoto's thyroiditis have been associated with improved outcomes in patients with DTC, potentially due to enhanced immune surveillance or altered tumor microenvironment dynamics.[26,27] This paradoxical protective effect suggests that chronic inflammation, under certain conditions, may modulate tumor behavior rather than uniformly promote progression.

Dietary iodine intake significantly influences the histological subtype distribution of thyroid cancer. Populations with iodine deficiency exhibit a higher prevalence of FTC, whereas iodine-sufficient regions report a predominance of papillary thyroid carcinoma (PTC).[28] The global decline in FTC incidence correlates with widespread iodine supplementation programs, highlighting the modifiable nature of this risk factor.[29] However, excessive iodine intake may also contribute to thyroid dysfunction and potentially influence cancer risk, underscoring the importance of balanced iodine nutrition.[30]

The marked female predominance in thyroid cancer incidence (F:M ratio ~3:1) implicates sex hormones and reproductive factors in thyroid carcinogenesis.[31] Estrogen receptor expression in thyroid tissue and experimental evidence of estrogen-mediated proliferation support a mechanistic role for hormonal signaling.[32] Paradoxically, while thyroid nodules are more common in women, nodules in men demonstrate a higher malignancy rate and are associated with more aggressive disease and increased cancer-specific mortality.[33] This suggests that biological sex modulates not only susceptibility but also tumor behavior and clinical outcomes.

Significant geographic and ethnic disparities in thyroid cancer incidence reflect the influence of environmental and lifestyle factors. For instance, age-standardized incidence rates vary from 2.5 per 100,000 in parts of Asia to over 15 per 100,000 in countries such as South Korea and the United States.[34] Regional clusters, such as elevated rates in Iceland and Hawaii, suggest contributions from genetic admixture, dietary patterns, environmental pollutants, or diagnostic intensity.[35] Migration studies indicate

that incidence patterns shift toward those of the host country within one to two generations, reinforcing the role of environmental over purely genetic determinants.[36]

While most thyroid cancers arise from interactions between genetic susceptibility and environmental triggers, ionizing radiation remains the most well-established and potent environmental carcinogen for both benign and malignant thyroid neoplasms.[37] Historical cohorts from atomic bomb survivors in Japan and populations exposed to radioactive fallout from the Chernobyl disaster provide unequivocal evidence of radiation-induced thyroid carcinogenesis, particularly in children.[38,39]

Ionizing radiation induces DNA double-strand breaks, which, if misrepaired, can lead to chromosomal rearrangements, point mutations, and genomic instability. The tumor suppressor protein p53 plays a central role in the DNA damage response by arresting the cell cycle at G1 to facilitate repair or, in cases of irreparable damage, initiating apoptosis.[40] In thyroid cells surviving radiation exposure, persistent genomic instability drives malignant transformation.[41]

Post-Chernobyl studies revealed that pediatric thyroid cancers exhibited a high frequency of *RET*/PTC rearrangements and marked genomic instability. A landmark analysis of 129 radiation-associated pediatric thyroid carcinomas demonstrated loss of heterozygosity or microsatellite alterations in 31% of cases, with the highest burden observed in girls exposed before age 9, who also developed more aggressive tumors.[42] These findings highlight the heightened radiosensitivity of the developing thyroid gland and the critical window of vulnerability during early childhood.

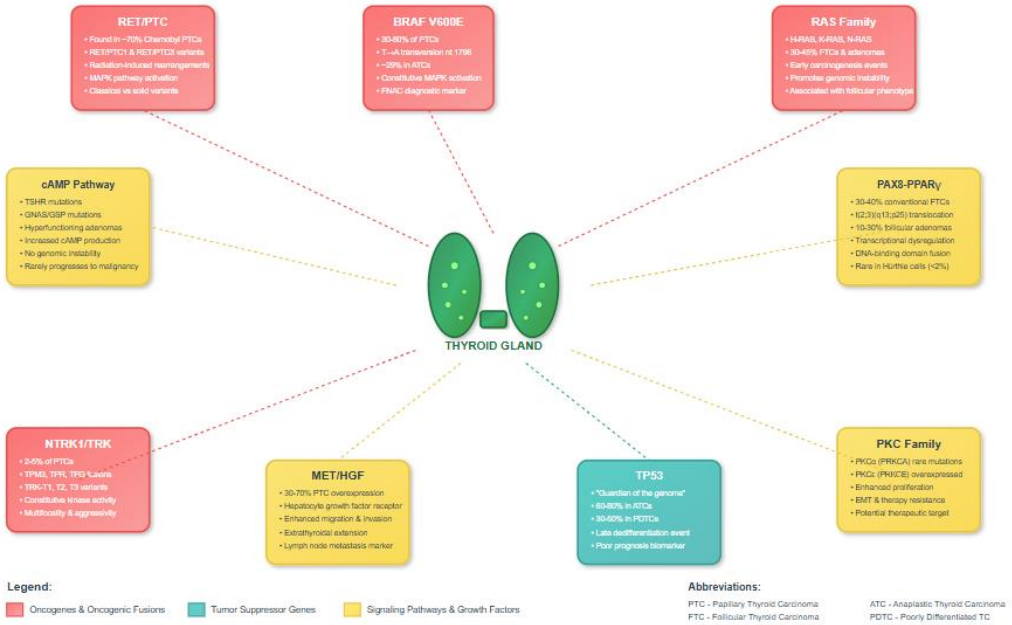
GENES INVOLVED IN THYROID TUMORIGENESIS

In unraveling the origins of thyroid cancer, one quickly encounters a mosaic of genetic players, each with distinct roles, yet often collaborating in quiet chaos. From the well-known drivers like *BRAF* and *RAS* in papillary and follicular tumors, to the fusion architects *RET*/PTC and *PAX8-PPARγ,* and the late-game disruptors like *TP53* in anaplastic disease, these genes do not just mutate; they rewrite cellular identity. Even lesser-known contributors, like *NTRK*, *MET*, and PKC isoforms, leave fingerprints on proliferation, invasion, or treatment resistance (Figure 6).

Multiple genes have been implicated in the complex and multistage progression of thyroid tumorigenesis, encompassing both spontaneous and radiation-induced neoplasms, as well as benign lesions such as goiters and adenomas; the phenotypic manifestation depends largely on clonal expansion patterns.[43] Recent studies have

identified mutations associated primarily with key oncogenic pathways and specific molecular abnormalities, involving cyclic AMP signaling, intracellular signaling cascades, and tyrosine kinase (TK) activity.[44]

Figure 6. Genes involved in thyroid tumorigenesis



Source: Study results

Within the adenylate cyclase/cAMP and phospholipase C pathways, activating mutations in the thyroid-stimulating hormone receptor gene (TSHR) and the alpha subunit of the stimulatory G protein gene (GNAS, historically referred to as GSP) are well documented, particularly in autonomously functioning thyroid adenomas. Constitutive activation of these pathways, driven by TSHR and GNAS mutations, is observed in the vast majority of hyperfunctioning thyroid nodules.[45] These mutations sustain increased cAMP production, promoting cellular growth, differentiation, and thyroid hormone synthesis, which culminates in hyperfunctioning adenoma development.[46] Importantly, such mutations do not induce genomic instability and thus do not predispose to oncogenic progression, explaining the lack of malignant transformation in these hot nodules.

In contrast, TSHR and GNAS mutations are infrequently associated with malignant thyroid neoplasms. The adenylate cyclase pathway accounts for mutations in autonomously functioning thyroid nodules, with TSHR and GNAS mutations being well established causes of toxic adenomas,[47,48] but their role in malignant transformation is limited. Proto-oncogenes within intracellular signaling pathways, such as the *RAS* family

(*H-RAS*, *K-RAS*, and *N-RAS*), are recurrently mutated in thyroid carcinomas and play critical roles in tumor initiation and progression. *RAS* mutations appear early in thyroid carcinogenesis; they contribute to genomic instability and facilitate the accumulation of subsequent genetic alterations. Their prevalence varies significantly: mutations in *RAS* genes occur, on average, in 30-45% of follicular thyroid cancer (FTC) and 30-45% of follicular adenomas.[49] In papillary thyroid cancers, *RAS* mutations are found in a subset of cases, particularly in follicular variant PTC.[50] The incidence of *RAS* mutation in FTC varies among studies ranging from 10.5% to 56.9%, which is higher than in follicular adenomas, where it ranges from 8% to 48%.[51] *RAS* mutations linked to the follicular phenotype occur frequently in sporadic thyroid tumors, accentuating their etiological importance in thyroid carcinogenesis.

Another fundamental mutation involves the *BRAF* gene, specifically the V600E substitution resulting from a thymine to adenine transversion at nucleotide 1796. This gain-of-function mutation is detected in approximately 30-80% of PTC cases, with prevalence varying between studies, commonly ranging from 37-48% and confers significant oncogenic capability by constitutively activating the MAPK pathway.[52,53] *BRAF* mutations have also been identified in subsets of ATC, with *BRAF* V600E mutations observed in approximately 29.4% of anaplastic thyroid carcinoma cases,[54] implicating them in advanced tumor progression and aggressiveness. Molecular detection of *BRAF V600E* via fine needle aspiration cytology has proven clinically valuable for diagnostic and prognostic stratification. Although false-negative rates have been reported, the test can increase the diagnostic accuracy of fine needle aspiration cytology.[55,56]

Activation of receptor TK pathways via gene rearrangements is chiefly represented by *RET*/PTC, TRK, MET, and PKC alterations. *RET* gene alterations serve as hallmark oncogenic events in PTC; rearrangements of the *RET* proto-oncogene are found in PTC and have been shown to play a pathogenic role, with the first *RET* rearrangement, named *RET*/PTC, which was discovered in 1987.[56,57] *RET* is normally not expressed in thyroid follicular cells. Specific codon mutations and chromosomal rearrangements form chimeric oncogenes such as *RET*/PTC, with the two most common rearrangement types being *RET*/PTC1 and *RET*/PTC3, both of which are intrachromosomal inversions involving the long arm of chromosome 10,[58] contributing to aberrant signaling that drives proliferation and survival. Studies demonstrate the presence of *RET* mutations in familial multiple endocrine neoplasia syndromes and sporadic medullary thyroid carcinomas (MTC). Multiple endocrine neoplasia type 2

(MEN2) is an autosomal dominant genetic syndrome caused by missense mutations in the *RET* proto-oncogene with different penetrance producing 3 variants, MEN2A, MEN2B, and familial MTC.[59,60] The *RET* protein comprises extracellular, transmembrane, and intracellular TK domains, with the kinase domain being essential for signal transduction. MEN2 mutations convert the *RET* proto-oncogene into a dominantly acting oncogene as a consequence of the ligand-independent activation of the TK.[61] In thyroid cancer, fusion of *RET*'s TK domain with various partner gene sequences generates oncogenic *RET*/PTC variants, with gene fusion being the first mechanism identified for the oncogenic activation of the receptor TK *RET* (Rearranged during Transfection), initially discovered in PTC, important in tumorigenesis.[62]

Upon exposure to ionizing radiation, the extracellular domain of the *RET*/PTC gene becomes substituted by sequences derived from other genes located either on chromosome 10 or on different chromosomes. The mechanism involves the spatial proximity of chromosomal loci during DNA damage, which brings partner genes close enough to enable illegitimate recombination.[63] To date, at least 10 different types of *RET*/PTC rearrangement variants have been characterized, with *RET*/PTC1 and *RET*/PTC3 being the most common types, accounting for more than 90% of all rearrangements found in PTCs,[64] each involving fusion of unique 5' partner gene segments with the transmembrane and TK domains of *RET*. A unifying mechanistic feature among these variants is the dimerization and constitutive activation of the *RET* receptor through chromosomal rearrangements that generate fusion genes, resulting in juxtaposition of the C-terminal region of *RET* with N-terminal portions of other proteins,[55] which triggers downstream signaling cascades including the MAP kinase and phosphoinositide pathways, with *RET*/PTC able to phosphorylate and activate phosphoinositide-dependent kinase 1 (PDK1).[65] This phenomenon is facilitated by ionizing radiation exposure, with evidence showing that *RET*/PTC rearrangements, particularly *RET*/PTC3, are highly prevalent in radiation-induced PTC, with prevalence ranging from 29% to 86% in radiation-induced cases,[66] enabling chromosomal rearrangements such as the classic *RET*/PTC3 fusion. Additional novel *RET*/PTC rearrangements continue to be identified as genomic profiling technology advances, including recently discovered variants such as HOOK3-*RET*.[67]

Clinically, specific *RET*/PTC rearrangements correlate strongly with thyroid tumors arising from distinct radiation exposures. *RET*/PTC3 rearrangement was the most frequently observed rearrangement in aggressive PTC that occurred in young children

soon after the Chernobyl accident, with RET activation found in nearly 70% of the patients who developed PTC following the Chernobyl accident,[68] demonstrating its role in radiation-induced tumor etiology. Conversely, *RET*/PTC1 rearrangement was more frequently observed in classical PTC that occurred later after the accident, and has been identified in thyroid tumors arising in populations exposed to low-dose external-beam irradiation in childhood.[69] Histopathologically, *RET*/PTC1 rearrangements are largely linked to the classical papillary phenotype,[70] whereas *RET*/PTC3 is more often observed in aggressive PTC variants,[71] which tend to be more aggressive and less common. The latency of tumor onset also differs by fusion type: the data suggest that *RET*/PTC3 may be typical for radiation-associated childhood PTC with a short latency period, whereas *RET*/PTC1 may be a marker for later-occurring PTC of radiation-exposed adults and children.[72] *RET*/PTC3 rearrangements confer a more aggressive tumor biology compared to *RET*/PTC1, with *RET*/PTC3 being associated with aggressive PTC.[73]

The strong association between *RET* molecular abnormalities and clinical outcomes in radiation-exposed thyroid tumors underscores *RET* rearrangements as principal genetic lesions implicated in radiation-induced thyroid carcinogenesis. A high frequency (approximately 60%) of *RET* rearrangements in Chernobyl PTC has been reported, with *RET* oncogene rearrangement being the most common oncogenic alteration in Chernobyl-related papillary thyroid cancer.[47] In this context, the involvement of the *NTRK1* gene, a neurotrophin receptor TK, is also implicated in thyroid carcinogenesis, though *NTRK1* rearrangements were rare (3.3%) in post-Chernobyl PTC. *NTRK1*-rearranged carcinomas showed a higher frequency of multifocality and aggressiveness following radiation exposure.[74,75]

Additional oncogenic TK receptor gene rearrangements include those involving the *NTRK1* gene, which are detected in approximately 2–5% of PTC.[76] These alterations arise from chromosomal translocations that juxtapose the TK domain of *NTRK1* with 5′ partner genes, such as *TPM3*, *TPR*, or *TFG*, resulting in the expression of chimeric *TRK* fusion proteins, including *TRK-T1*, *TRK-T2*, and *TRK-T3*. These fusion proteins exhibit ligand-independent constitutive kinase activity, driving oncogenic transformation and tumor progression.[77]

Separately, the *MET* proto-oncogene, encoding the receptor for hepatocyte growth factor (HGF), is frequently overexpressed in both papillary and ATC. Sustained *MET* activation, whether through transcriptional upregulation, gene amplification, or autocrine HGF signaling, promotes mitogenic, migratory, and invasive phenotypes.

Immunohistochemical analyses report *MET* overexpression in 30–70% of PTCs, where it correlates with aggressive clinicopathological features, including extrathyroidal extension, lymph node metastasis, and disease recurrence, underscoring its role as a biomarker of tumor progression and a potential therapeutic target.[78,79]

Fusion genes involving *PAX8* and *PPARγ* are recurrent molecular alterations predominantly associated with FTC. The *PAX8-PPARγ* rearrangement results from a t(2;3)(q13;p25) translocation, fusing the DNA-binding domains of *PAX8* to the majority of the *PPARγ* coding sequence, generating a chimeric protein that dysregulates transcriptional programs involved in differentiation and proliferation, thereby promoting oncogenesis.[80]

While historically reported in up to 50–60% of FTC, more recent and methodologically rigorous studies — including next-generation sequencing and multi-institutional cohorts — indicate that *PAX8-PPARγ* is detectable in approximately 30–40% of conventional FTCs, with significant geographic and methodological variability.[81,82] Importantly, this fusion is not exclusive to malignancy: it is also found in 10–30% of follicular adenomas, challenging its utility as a standalone diagnostic marker to distinguish benign from malignant follicular neoplasms.[83] In Hürthle cell carcinomas, *PAX8-PPARγ* rearrangements are exceedingly rare (<2%), and their presence may reflect misclassification or overlap with oncocytic variants of FTC rather than true Hürthle cell lineage.[84]

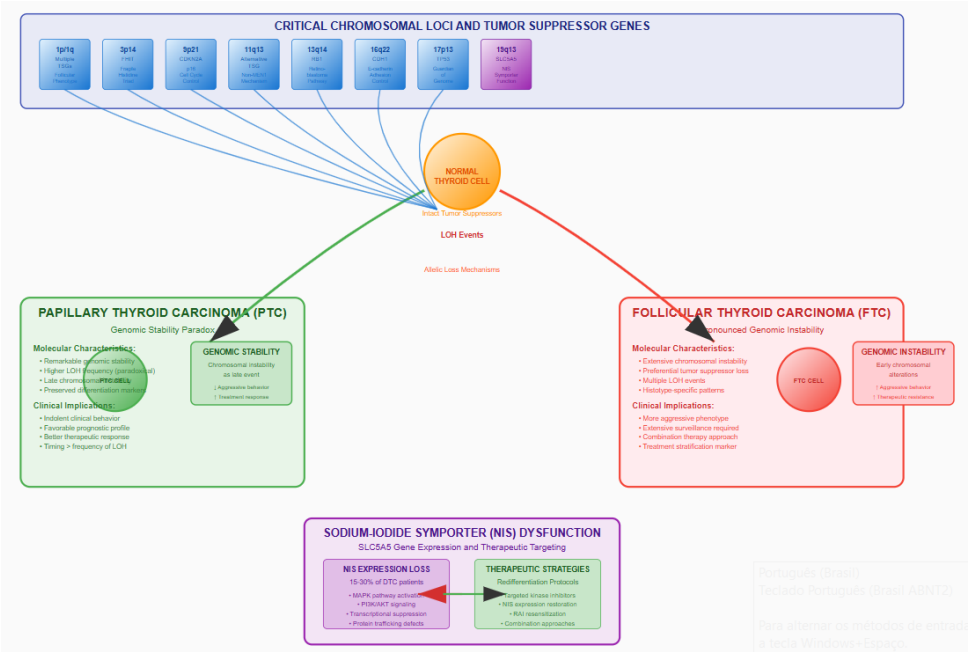
Finally, the tumor suppressor gene *TP53* often termed the “guardian of the genome”, encodes a master transcriptional regulator activated in response to DNA damage, oncogenic stress, or hypoxia. Upon activation, p53 orchestrates cell cycle arrest, DNA repair, senescence, or apoptosis, thereby preserving genomic integrity.[85] In thyroid cancer, *TP53* mutations or functional inactivation are rare in well-differentiated carcinomas but become highly prevalent in advanced disease: they are detected in 60–80% of ATC and 30–50% of poorly DTC, where they serve as molecular hallmarks of dedifferentiation and aggressive behavior.[86,87] Although *TP53* alterations typically represent late events in thyroid carcinogenesis, often coinciding with loss of iodine avidity and resistance to conventional therapies, their presence is strongly associated with reduced survival, increased metastatic potential, and therapeutic resistance, making them critical prognostic biomarkers and emerging targets for precision oncology approaches.[88,89]

Beyond canonical MAPK and PI3K-AKT pathways, dysregulation of the protein kinase C (PKC) family contributes to thyroid tumorigenesis through isoform-specific mechanisms. While genetic mutations in the PRKCA gene (encoding PKCα) are exceedingly rare in thyroid carcinomas, functional studies indicate that PKCα activity may still be modulated by upstream signals in tumor cells.[90] In contrast, the epsilon isoform (PKCε, encoded by PRKCE) is consistently overexpressed in papillary and anaplastic thyroid cancers, where it drives oncogenic phenotypes including enhanced proliferation, evasion of apoptosis, epithelial-mesenchymal transition, and resistance to therapy.[91] Preclinical models demonstrate that PKCε knockdown suppresses tumor growth and invasion, confirming its functional role as an oncogenic driver rather than a passive bystander.[92] Thus, PKCε represents not only a biomarker of aggressive disease but also a potential therapeutic target in advanced thyroid cancer.

TUMOR SUPPRESSOR GENE NETWORKS IN THYROID CARCINOGENESIS

The complex landscape of tumor suppressor gene dysfunction fundamentally underpins the pathogenesis of thyroid neoplasia, with distinct patterns of genomic instability characterizing different histological phenotypes. Contemporary molecular analyses reveal that tumor suppressor gene alterations exhibit preferential associations with specific thyroid cancer subtypes, particularly demonstrating pronounced involvement in follicular-derived neoplasms (Figure 7).[93]

Figure 7. Tumor suppressor gene networks in thyroid carcinogenesis



Source: Study results

The phenomenon of allelic loss, manifested through loss of heterozygosity (LOH), represents a cardinal mechanism underlying tumor suppressor gene inactivation in thyroid carcinogenesis. Paradoxically, while LOH events occur with greater frequency in FTC, PTC demonstrates remarkable genomic stability relative to its follicular counterpart.[94] This genomic stability paradox in PTC correlates with its characteristically indolent clinical behavior and favorable prognostic profile, suggesting that genomic instability represents a later evolutionary event in papillary tumor progression rather than an initiating mechanism.[87]

Beyond the well-characterized *TP53* pathway, contemporary genomic investigations have identified multiple chromosomal regions harboring putative tumor suppressor genes critical for thyroid follicular cell homeostasis. Particularly significant are the genomic loci at 11q13, 9p21 (CDKN2A/p16), 13q14 (RB1), 3p14 (FHIT), 17p13 (*TP53*), and regions within 1p/1q, which demonstrate recurrent allelic losses predominantly in follicular phenotype neoplasms.[95] The 11q13 region, while initially investigated for MEN1 gene involvement, appears to harbor alternative tumor suppressor mechanisms, as mutations in MEN1 itself are infrequently observed in sporadic thyroid tumors.[96] Recent molecular profiling studies have expanded our understanding of the E-cadherin (CDH1) tumor suppressor located at 16q22, revealing significant correlations between LOH events and aggressive tumor characteristics in both papillary and follicular carcinomas.[97] The FHIT gene at 3p14 represents another critical tumor suppressor, with LOH studies demonstrating distinct patterns of loss across different thyroid tumor types, suggesting histotype-specific mechanisms of genomic instability.[98]

The sodium-iodide symporter (NIS), encoded by the SLC5A5 gene, occupies a distinctive position in thyroid cancer biology, functioning simultaneously as a differentiation marker and therapeutic target. Contemporary clinical data indicate that approximately 15-30% of patients with DTC exhibit reduced or absent NIS expression, fundamentally compromising the efficacy of radioactive iodine therapy.[99] This loss of NIS function represents a critical clinical challenge, as it precludes both ablative treatment with I-131 and subsequent molecular imaging for disease surveillance.[100] The molecular mechanisms underlying NIS downregulation involve complex signaling pathway alterations, including aberrant activation of the MAPK and PI3K/AKT pathways, which interfere with both NIS gene transcription and protein trafficking to the cell membrane.[101] Recent therapeutic investigations have focused on redifferentiation strategies employing

targeted kinase inhibitors to restore NIS expression and function, thereby resensitizing tumors to radioiodine therapy.[102]

The contemporary understanding of tumor suppressor gene networks in thyroid cancer has profound implications for personalized medicine approaches. The genomic stability observed in PTC, which is paradoxically associated with better clinical outcomes despite the presence of LOH events, challenges traditional concepts linking genomic instability directly to aggressive behavior.[81] This observation suggests that the timing and context of tumor suppressor gene loss, rather than simply the frequency of such events, determines clinical phenotype. Furthermore, the identification of specific LOH patterns correlating with tumor differentiation status has emerged as a potential biomarker for treatment stratification. Patients with tumors exhibiting extensive genomic instability, particularly involving multiple tumor suppressor loci, may require more aggressive therapeutic approaches and intensive surveillance protocols.[103]

The integration of comprehensive genomic profiling with functional studies of tumor suppressor pathways continues to reveal the complexity of thyroid carcinogenesis. Understanding of complex relationship between genomic stability, differentiation status, and clinical behavior will likely inform next-generation therapeutic strategies, including combination approaches targeting multiple pathways simultaneously and novel redifferentiation protocols for radioiodine-refractory disease.

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.

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Este preprint foi submetido sob as seguintes condições:

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