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GENETIC INSIGHTS INTO THYROID TUMOR PROGRESSION: FROM ADENOMA TO ANAPLASTIC CANCER

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ABSTRACT:
Background: Thyroid neoplasms exhibit a diverse evolutionary trajectory, suggesting distinct pathways from normal thyroid cells to malignancy.
Methods: Molecular changes initiating follicular adenoma formation likely precede progression to follicular cancer. Papillary carcinoma, however, may evolve via a separate pathway, bypassing follicular adenoma. Subsequent genetic alterations can lead to anaplastic cancer, significantly impacting prognosis.
Results: Genome instability predisposes thyroid tumour cells to molecular alterations, with proto-oncogene changes occurring early and suppressor gene mutations typically occurring later. These changes contribute to aggressive or invasive behaviours, potentially influencing clinical outcomes.
Conclusion: Advances in understanding genetic alterations in thyroid oncogenesis offer promise for enhancing diagnostic accuracy and treatment efficacy, thereby improving outcomes for thyroid malignancies.

KEYWORDS: Thyroid Carcinoma, Molecular Markers, Thyroid neoplasms, Follicular adenoma, Follicular cancer, Papillary carcinoma, Anaplastic cancer, Genome instability, Diagnostic accuracy, Treatment efficacy.

INTRODUCTION:

In a recent review, Hanahan and Weinberg[1] summarize the correlation of events that occur in neoplasia development. These authors propose that for the oncogenic process to take place, six essential functions of cellular physiology must be altered: a) self-sufficiency to govern growth signals (where proto-oncogenes have a predominant mission), b) insensitivity towards signals inhibitory of cell growth (mediated especially by tumour suppressor genes), c) evasion of cell death (apoptosis), d) unlimited replicative potential, e) sustained promotion of angiogenesis and f) alterations in cellular adhesiveness that would provide capacity for tissue invasion and the development of metastasis (Chiba 2024).
These changes may be due to genetic alterations, many of which have yet to be elucidated. These six events generally occur in a cell with some genetic instability.

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Among these traits, the genetic changes determining the alteration in the expression of proteins involved in cell replication are particularly relevant. In this sense, two large groups of genes stand out: proto-oncogenes and tumour suppressor genes. The former condition the appearance of signals that lead to cell proliferation, while the latter play the opposite role. The expression of both gene types responds to transmembrane receptor activation and, therefore, depends on extracellular signals. The mutation of proto-oncogenes will lead to the appearance of oncogenes with the capacity to mimic these signals. Tumour suppressor genes generally drive the cell toward a quiescent state (G0) in a postmitotic

situation after differentiation. Its alteration is usually a late event in the evolution of the oncogenic process and determines that the cell replication process stimulated by oncogenes does not stop (Rodrigues, Da Cruz Paula et al. 2024).

Classification of thyroid carcinoma.

Interest in molecular studies

The morphological division of malignant thyroid neoplasms is classic based on their cellular origin (follicular or parafollicular) or their differentiation (papillary, follicular, poorly differentiated, and undifferentiated). It is worth asking whether this classification responds adequately to the information provided by current knowledge or whether we are in a position to delve into the molecular cataloguing of these neoplasms. The advance in this new classification of thyroid neoplasms may offer other perspectives that allow for increasing the effectiveness of diagnostic and therapeutic procedures (Gulec and Meneses, 2024).

The oncogenic process is an open phenomenon subject, by its very nature, to constant molecular changes of both a genetic and epigenetic nature. In all probability, in any thyroid carcinoma (TC), regardless of its histological classification, the collection of oncogenic phenomena outlined by Hanahan and Weinberg is followed.[1]. However, to date, it has not been possible to establish the molecular bases that lead to the appearance of the different cellular phenotypes, nor what genetic changes can condition the evolution towards a pattern of cellular differentiation, although the efforts are notable. What is being done in this regard? The experimental data provide strong signals to suspect that the change from a differentiated to an undifferentiated neoplasm occurs without interruption due to the accumulation of deleterious mutations (Wang, Zhang et al. 2024).

It is currently being studied using microarray CT specimen techniques to search for the association between a gene expression pattern and the different oncological profiles of follicular cells. Recently, the genetic expression profile has been studied in CF tissue and in its brain metastases.[7]. It has been observed that in the metastatic tissue, there was an overexpression of 18 genes and a decrease in expression in 40. The genes that showed altered expression were related to cell cycle regulation, apoptosis, DNA repair, angiogenesis, cell adhesion, motility, invasiveness, and the immune response. These authors observed that the pattern of gene expression in the primary tumour and the metastasis was different (Shobab, Zheng et al. 2024).

Oncogenesis and mutations in thyroid carcinoma*Generalities*

Some TCs seem to be characterized by genetic instability (hypermutability), which leads to the accumulation of mutations or changes in the DNA that will give rise to different neoplasms. It is also speculated that the change in the DNA methylation pattern may be an early event in carcinogenesis, and this may contribute, among other things, to said genetic instability.[8]. In turn, this alteration would help explain the progression from differentiated carcinoma to IC (Murugan, Al-Hindi et al. 2024).

Specifically, genetic lesions such as rearrangements and chromosomal translocations are involved in CT, exceptional aspects in many other epithelial tumours.[13]. Thus, some regroupings have been described as *correct/PTC*(typical of papillary neoplasms), *NTRK y Pax-8/ PPARg,* the latter being characteristic of CF since it is found in up to 62% of these tumours, without being present in CP[14]. As an empirical observation, it has been described that there is an alteration in the DNA repair mechanism in PC, which will give rise to microsatellite instability. This aspect contributes to tumour development and progression. Likewise, it has also been observed that there are various epigenetic phenomena, such as the deamination of CpG dinucleotides in poorly differentiated carcinomas, which are associated with tumour progression or methylations in the gene.*p16*in up to 33% of cases (Turner, Hamidi et al. 2024).

In the development of thyroid neoplasms, other alterations also occur that condition the synthesis of defective proteins without implying a mutation in the corresponding gene. Thus, splicing alternatives are developed in some suppressor genes, such as *FHIT (fragile histidine triad gene)* and *TSG 101 (Tumour suppressor gene 101)*[17]. This alteration entails a different grouping of the codons that make up the different exons and introns and, therefore, a different mRNA, whose translation will condition the synthesis of a modified protein. However, it has not been possible to establish precisely the consequences caused by the *splicing* alternatives, although they do not seem to be related to the stage or the degree of differentiation of these tumours. These alterations are found in both benign and malignant neoplasms, indicating that they may constitute an early event in developing thyroid neoplasms (Liu, Jiang, et al. 2024).

Table 1: References on Oncogenic Processes and Genetic Alterations

Reference	Description
Hanahan and Weinberg, 2021	Summarizes the six essential functions altered in neoplasia: growth signal autonomy, insensitivity to growth inhibitors, evasion of apoptosis, replicative immortality, sustained angiogenesis, tissue invasion and metastasis.
Chiba, 2024	Discusses the role of genetic alterations in cellular adhesion and metastasis development.
Rodrigues, Da Cruz Paula et al., 2024	Highlights proto-oncogenes and tumour suppressor genes in regulating cell proliferation and differentiation.
Gulec and Meneses, 2024	Proposes molecular categorization of thyroid neoplasms for improved

	diagnostic and therapeutic approaches.
Wang, Zhang et al., 2024	Investigates genetic changes contributing to differentiation patterns and oncogenic evolution in thyroid carcinoma.
Shobab, Zheng et al., 2024	Studies gene expression profiles in thyroid carcinoma and its metastases, revealing differences in genetic regulation between primary and metastatic tumours.
Murugan, Al-Hindi et al., 2024	Explores genetic instability and DNA methylation patterns as early events in thyroid carcinogenesis.
Turner, Hamidi et al., 2024	Examines chromosomal rearrangements, DNA repair mechanisms, and epigenetic phenomena in thyroid carcinoma progression.
Liu, Jiang et al., 2024	Investigates splicing alterations in suppressor genes and their implications in thyroid neoplasms.
Califano, Smulever et al., 2024	Studies mutations in oncogenes (such as RAS, RET, TRK, MET, PTEN) and suppressor genes in thyroid adenoma and carcinoma development.

Table 2: Classification and Molecular Studies in Thyroid Carcinoma

Reference	Description
Hanahan and Weinberg, 2021	Provides a theoretical framework for understanding oncogenic processes in various types of thyroid carcinoma.
Wang, Zhang et al., 2024	Investigates the association between gene expression patterns and oncological profiles in follicular cells using microarray techniques.
Wang, Zhang et al., 2024	Compares gene expression profiles between primary thyroid tumours and their brain metastases, revealing significant differences.

Table 3: Genetic Lesions and Molecular Pathways in Thyroid Carcinoma

Reference	Description
Wang, Zhang et al., 2024	Discusses genetic lesions such as rearrangements and chromosomal translocations in papillary thyroid carcinoma.
Turner, Hamidi et al., 2024	Explores DNA repair mechanisms and epigenetic alterations contributing to tumour development and progression in thyroid carcinoma.
Liu, Jiang et al., 2024	Investigates alternative splicing in genes like FHIT and TSG101, potentially influencing protein synthesis and tumour development in thyroid neoplasms.

Table 4: Genetic and Epigenetic Changes in Thyroid Carcinoma

Reference	Description
Murugan, Al-Hindi et al., 2024	Discusses hypermutability, accumulation of mutations in thyroid carcinoma, and changes in DNA methylation patterns.
Turner, Hamidi et al., 2024	Explores chromosomal rearrangements, DNA repair mechanisms, and epigenetic phenomena like CpG dinucleotide deamination in thyroid carcinoma progression.
Califano, Smulever et al., 2024	Studies mutations in oncogenes (RAS, RET, TRK, MET, PTEN) and suppressor genes in thyroid adenoma and carcinoma development.

Table 5: Molecular Classification and Diagnostic Perspectives in Thyroid Neoplasms

Reference	Description
Gulec and Meneses, 2024	Discusses the morphological and molecular classification of thyroid neoplasms, emphasizing the potential for improved diagnostic and therapeutic strategies.
Wang, Zhang et al., 2024	Examines gene expression profiling in distinguishing different oncological profiles of thyroid tumours and their metastases.
Shobab, Zheng et al., 2024	Investigates differential gene expression between primary thyroid tumours and metastatic tissues, highlighting potential diagnostic markers.

\Table 6: Oncogenic Processes and Key Genetic Alterations

Reference	Description
Hanahan and Weinberg, 2021	Summarizes the six essential alterations in cellular physiology for oncogenic processes, including growth signal autonomy and evasion of apoptosis.
Rodrigues, Da Cruz Paula et al., 2024	Explores the roles of proto-oncogenes and tumour suppressor genes in regulating cell proliferation and differentiation in thyroid carcinoma.
Liu, Jiang et al., 2024	Investigates alternative splicing in suppressor genes FHIT and TSG101, potentially influencing protein synthesis and tumour development in thyroid neoplasms.

Little is known about the genetic changes determining the beginning of adenoma development and its transition to carcinoma. In some cases, the activation, mutation, or expression of one of some oncogenes or growth factors such as *race, right, TRK, met y PTEN*or the TSH receptor (TSH-R). In contrast, mutations of suppressor genes may appear (Tables 1, 2 and 3). As has been outlined, the procession of mutations (Califano, Smulever, et al. 2024).

Table 1. Genetic changes detected in follicular thyroid carcinoma

Gen	Gen class or function	Disturbance	Type of Neoplasm	Time
TSH-R	Receptor TSH	Mutation	Hyperfunctioning adenoma and carcinoma	
Activina A-R	Activin A Receptor	Underexpression	CP	
TGFb-R	A receptor for TGF-β	Underexpression	CP	
ADN mitochondrial	CP and Hürthle cell mutation	*do a*poptosis receptor	Overexpression of CP, CF, and Hürthle cells	
Fas	Pro-apoptótica	Underexpression	CP, CF and Hürthle cell	
ICAM-1	Adhesion molecule	Overexpression	Carcinoma	
cateninas a, b, g	Adhesion molecule	Underexpression	Adenomas and carcinomas	Late
Mutation	Carcinoma			
And cadherin	Adhesion molecule	Underexpression		
Galectina 3	Adhesion molecule	Overexpression in cytoplasm	Carcinoma	
CD44v6	Adhesion molecule	Underexpression (?)	Carcinoma	
VEGF	Angiogenic factor	Overexpression	Carcinoma	
EGF	Growth factor	Overexpression	Carcinoma	
NIS	Iodine transport	Underexpression.	Carcinoma	Late
Epigenetic changes				
Pendrina	Iodine transports	Underexpression	THERE.	
Tiroglobulina	Synthesis supports	the Underexpression	of the THERE	Late thyroid hormones.
TTF-1	Transcription factor	Underexpression	CP, CF, and CI	Late
TTF-2	Transcription factor	Underexpression	CI	Late
Pax-8	transcription factor	Underexpression	CP, CF y CI	Late
Pax-8-PPARg	Factor clustering	Underexpression	AF, CF, and CI	Intermediate transcription
nm23-H1	metastasis suppressor gene	Underexpression	CF	
SEE	Proapopotic molecule	Overexpression	CP	

contributes to the development of neoplasia and is not limited to proto-oncogenes or suppressor genes. Any phenomenon that is related to proliferation falls within the scope of oncogenesis. Thus, for example, it is known that TGF-band Activin A is probably the most critical inhibitor of average follicular cell growth. Therefore, it is not surprising that the resistance of tumour cells to the action of these elements has been described. It has been found that CP thyrocytes have a lower expression of TGF-receptors. b, and changes have also been found in the expression of the Activin A receptor (Ray, Sable et al. 2024).

The presence of somatic mutations of mitochondrial DNA has also been detected in CP and Hürthle cell carcinoma cells, which indicates that said alteration may be present in the development of this type of neoplasm and may condition the progression of said tumours. However, the extent of these findings currently remains elusive. A characteristic of every neoplasm is its ability to evade immune surveillance. This property is related, among other mechanisms, to the ability of tumour cells to express Fas-L and thus activate the Fas receptor (CD 95) of immune cells, inducing their apoptosis. This ligand has been observed in both CP and CF cells. On the contrary, its expression is weak or absent in medullary carcinoma cells. Furthermore, tumour cells are observed to protect themselves from a possible "fratricidal" action by weakly expressing Fas (Kalfert, Ludvikova et al. 2024).

The membrane protein CD 97 or GR1 is generally expressed in activated lymphocytes, binding to CD 55 or DAF: cell deterioration acceleration factor. CD 97 has recently been assigned a role as a cell differentiation marker. This molecule is not expressed in the normal thyroid gland; however, it is detected in neoplasms without having a clear correlation with the tumour stage. Similarly, a connection has been established between the activity of type 1 deiodinase and cell differentiation since its activity is high in healthy thyroid tissue. At the same time, it is low in differentiated CF and practically undetectable in IC. Among all these alterations, the changes in proto-oncogenes and tumour suppressor genes are of capital importance due to their importance in regulating cell replication.

Roto-oncogene mutations. An early phenomenon

The ras proto-oncogene mutations have been implicated in the initial stages of development of various tumour types and occur in approximately 10-15% of all human carcinomas. There are three types of ras proto-oncogenes*(H race, K race, and N race)*. The activating ras mutation is probably an early phenomenon in the evolution of thyroid neoplasms. Experimentally, it has been observed that this alteration destabilizes the genome of the PCCL3 thyroid cell line, which is consistent with the beginning of the neoplastic process since, functionally, this proto-oncogene promotes phenotypic progression. A failure in its function leads to the predisposition of large-scale genomic abnormalities. It has been seen

that there is a specific correlation between the presence of the ras mutation and the age of presentation since they are rare in thyroid neoplasms that occur in the young population, while their prevalence increases as age advances. This mutation is more frequent if there has been a history of radiation. The information available is consistent with the hypothesis that initially, the ras mutation would condition the development of FA and subsequently that of other neoplasms. (Table 2) (Tous, Muñoz-Redondo et al. 2024).

It is observed that between 5-20% of PCs present this mutation, although there is also an increase in the expression of this proto-oncogene in this tumour type. Between 24-53% of CF have mutations in this proto-oncogene, and its expression can increase by up to 53% of cases. Furthermore, it has been seen that proto-oncogene mutations are more common in FCs that present metastases. The prevalence of mutations in IC ranges between 20-60% and their expression increases by up to 60% in these tumours. Although some authors have not been able to establish a clear relationship between the presence of ras mutations and the aggressiveness of the tumour, others have managed to correlate the existence of mutations in codon 61 of *race* with the differentiation of the CT (Higgins, Sadow, et al. 2024).

This mutation is not usually found in medullary carcinomas. *CCND1, erbB2, and three proto-oncogenes are* frequently altered in solid neoplasms. The expression of these genes has been studied in CT tissue specimens, and the frequency of their expression has been observed to be variable. Some authors point out that *erbB2* is overexpressed in CP but is rarely mutated in this.

Type of neoplasms, and on the other hand, it has been seen that there is a poor expression oferbB232 in CF and IC. However, *CCND1* is overexpressed in both malignant and benign neoplasms. Data on increased expression of*myc* They are contradictory. The set of these results indicates that in the development of TC, the mutations of *CCND1* may have an early role while *they* would be altered later (Soboska, Kusiński, et al. 2024).

The study of the proto-oncogene *HGF (hepatocyte growth factor)* and its receptor HGF-R (or*c-met*) helps explain some of the events that make up the natural history of thyroid neoplasms. Said proto-oncogene is overexpressed, but not mutated, in AF and CP[33]. However, this situation may result from previous mutations since it has been seen that the increase in ras activity and *the suitable* conditions cause the accumulation of MET RNA. In other words, the lack of regulation may result from different molecular pathways capable of inducing thyroid cell transformation. Cells with increased expression can produce and activate HGF.

Interestingly, no expression of HGF or c-met has been found in either the CF or the IC. This deficiency is related to the loss of genetic material of chromosome 7q since this absence is not found in AF or CP with good evolution but is present in those with a poor prognosis. The proto-oncogene*TRK* encodes a membrane tyrosine kinase that acts as a neuronal growth factor receptor. It has also been seen that in the CP, it is often activated *N-TRK1* (also known as*TRKA*, located at 1q22). As in the ret proto-oncogene case, this gene's activation is caused by reassortments in which at least three genes are involved (Ju, Sun et al. 2024).

Ret: an emblematic proto-oncogene of the thyroid

Proto-oncogene activation-*right* It has been related to the development of CP (follicular lineage) and medullary carcinoma (C cell), but its contribution to the development of both neoplasms takes place differently. In CP, there are somatic regroupings of the *right*, with various activated genes contributing to the expression of the chimeric RET/PTC oncoproteins. At the same time, in spinal cord tumours, there are mutations in the germ line, frequently punctual, that lead to the constitutional activation of the tyrosine kinase function. RET is fundamentally responsible for the development of multiple endocrine neoplasia type 2 (MEN 2) Clusters of the ret proto-oncogene (10q11.2) are probably the most frequently found somatic genetic changes (10-40%) in thyroid PCa. Eight types of regroupings (inversions and translocations) of *rights* have been identified as RET/PTC1 to RET/ PTC8 (Smith, Frye et al. 2024).

At the same time, attempts have been made to associate specific RET/PTC mutations with various factors, such as exposure to radiation, age, and even histological variants of PC, without establishing firm conclusions. There is no consensus on the presence of the mutation and its relationship with the biological behaviour of the neoplasia or its response to treatment. At the moment, these supposed relationships lack practical implications. In this attempt to correlate the prognosis of PC with the presence of RET/PTC regroupings, it has been seen that half of PCs show RET-TK (RET with tyrosine kinase domain), of which only a tiny part is explained by the regrouping of RET/PTC (Yu, Liu et al. 2024).

PTC. On the contrary, the expression of *wild-type ret* It has been detected in 45% of RET-TK positive tumours, and its expression was an independent risk factor for aggressive PC. In this sense, it is also worth noting that some authors have observed that RET/PTC1 regrouping is associated with a more aggressive clinical course in adults. This regrouping is more frequent in patients who undergo external radiation. And it seems that prolonged radiation exposure is associated with a change from RET/PTC3 to RET/PTC1. Two new gene fusions have recently been identified involving the *right.* These are ELKS and PCM-1. Notably, IC or CF have not described RET regroupings (Tables 2 and 4) (Iacobas and Iacobas 2024).

Mutations of the p53 suppressor gene. A late event

The action of the P53 protein is not only decisive in the process of cell proliferation, but other fundamental properties are attributed to it, such as the organization of the repair of errors in DNA replication. It is understood that the failure of this mechanism can decisively condition the development of the neoplasia (Tables 3 and 4). It has been proven that in CT, the suppressor gene*p53* is hypermutable· The percentage of the different mutations found suggests that they occur

at random. These mutations appear to be a late event in the multistep pathogenesis of neoplasia development, which is why they constitute a trait indicative of poorly differentiated tumours or IC. The expression of *p53*It is increased in 11% of PC, 14% of CF, 25-41% of poorly differentiated carcinomas, and 64% and 71% of IC (Lasolle, Schiavo et al. 2024).
This increase in expression occurs without it, meaning mutations in the corresponding gene are present. Instead, the increase in expression can indicate two phenomena. Firstly, the existence of probable alterations or mutations of genes that encode proteins that condition, by various mechanisms, increases the expression of P53. It may also occur that alterations take place in the synthesis of some of the proteins of the metabolic chain that is activated by this fundamental suppressor gene; This would condition impotence in the function of P53 and, therefore, its corresponding intracellular accumulation (Guan, Wang et al. 2024).
As mentioned, there is a clear correlation between the presence of mutations or changes in this gene and the tumour's aggressiveness, which is consistent with the loss of the biological function of the suppressor gene.*p53*. Lacking an adequate control mechanism that regulates the correction of errors in the DNA synthesis and repair process increases the probability of new mutations occurring after each cell division opens up. This probability is increased if, as happens in neoplasms, there is an increase in cell proliferation. This alteration can also lead to the development of new clones with specific and diverse mutations compared to others that may be developing in the same tumour from a neoplasm with the exact clonal origin (DeBoy, Nicosia, et al. 2024)
It is also worth noting that loss of heterozygosity has been found in *p53* in samples of the high cell variant of CP but not in samples of classic CP, which is related to the worse prognosis of that tumour subtype. Likewise, mutations have been found*p53*in up to 38% of CP with an insular component, which, as is known, is associated with a worse prognosis. And worryingly, it is found that in more than 75% of ICs mutations of the*p53*[27,59,60], so this alteration plays a vital role in the clinicopathological behaviour of CT (Wang, Zhang et al. 2024).
Ten years after the Chornobyl accident, the presence of mutations of *p53* in CT samples from subjects who were subjected to radiation. The results suggested that mutations in codons 167 and 183 could play an essential role in the pathogenesis of this subtype of CP secondary to radiation. However, other authors are reluctant to admit that radiation plays a role in increasing the mutation rate of *p53*. However, it has been speculated that treatment with me in patients who have mutations in *p53* can cause evolutionary changes in differentiated tumours, favouring their transformation into undifferentiated tumours (Sun, Zhao, et al. 2024).

Other suppressor gene mutations

It has been seen that the highly malignant phenotype of IC has a recessive character. That is, it seems that the development of IC is due, to a greater extent, to the failure of tumour suppressor genes (which have a recessive character) than to the activation of oncogenes whose expression follows the rules of dominant characters Tables 3 and 4). *PTEN* is a tumour suppressor gene that encodes the expression of a phosphatase. Loss of heterozygosity of 10q23 (the locus of *PTEN*) is found in 5-21% of CP, 7-30% of CF, and 35-59% of IC, negatively correlated with the expression of the PTEN protein. Therefore, it is usually underexpressed in these neoplasms. Mutations are rarely found.
It has also been seen that the expression of*ten* may act as a suppressor of carcinogenesis (Guo, Sun et al. 2024),Since re-expression of the gene in cell lines inhibits tumour growth, a close relationship has been described between the expression of *PTEN* and the cyclin-dependent kinase inhibitor p27-kip1. From the above, it is concluded that the inactivation of *PTEN* may play a role in the development of spontaneous TC, especially CF, where mutations of *PTEN are* in 8% of these carcinomas. It is interesting to remember that this suppressor gene plays a fundamental role in Cowden's disease, where benign thyroid neoplasms frequently coexist with multiple hamartomas and breast neoplasms.
It has also been seen that the alteration in the suppressor gene is associated with a late process and, therefore, with the most aggressive and undifferentiated types of cancer (Zhao et al. 2024).

Role of TSH in the morphological and functional control of thyrocytes

There is open controversy about the contribution of mutations in the TSH receptor to thyroid oncogenesis. Some authors do not find that it has a role in the development of differentiated carcinoma, while others affirm that point mutations in the TSH-R and Gs are oncogenic. Isolated TSH-R mutations have been found in hyperfunctioning CP. A somatic TSH-R mutation has also been described in CF tissue, which may explain the rarity of thyroid hyperfunction associated with these tumours. However

Alterations in adhesion molecules: indicators of aggressiveness

The thyrocyte does not detect the expression of intercellular adhesion molecule 1 (ICAM-1). This expression can be stimulated by a wide variety of factors that interact with the immune system, such as proinflammatory cytokines interferon-c(IFN-c), tumour necrosis factor (TNF-a), interleukin-1 (IL-1), and retinoic acidic-1 is overexpressed in thyroid neoplasms, which is speculated to contribute to the tumour evading the action of the immune system (Xu, Viswanathan, et al. 2024).
The catenins (-a, -b, and -c) are a group of cytoplasmic proteins whose expression is ubiquitous, to which a crucial role is attributed in cell-cell adhesion mediated by E cadherin. Specifically, these proteins link the cytoskeleton with the extracellular adhesion system. It is known that the reduction of E-cadherin expression darkens the prognosis of TC. However, it seems that the lack of expression of catenins better reflects the future evolution of the neoplasia. It has been seen that the expression of these three proteins is decreased in thyroid carcinomas. Likewise, relationships have been

established between traits that condition the prognosis of tumours with the expression of these molecules. Thus, it has been observed that there is a correlation between the decrease in expression of catenins -A and -with increasing age at diagnosis and TNM stage. Tumour size has been related to reduced catenin expression. Band -c. There is a relationship between lymph node metastases nares and the reduction of catenin-a, while distant metastases are more frequent if the expression of -band -c. Tumour recurrence is in tune with a lower presence of catenin-a, while mortality is higher in tumours with decreased expression of –b (Amjad, Asnaashari et al. 2024).

These findings make it advisable to estimate catenin expression. aas a prognostic indicator[79]. It is thought that catenin-bIt can also act as an oncogene in TCs. This assumption is supported by the finding, in neoplasms, of heterotopic nuclear expression. The location of catenin-intranuclear is restricted to poorly differentiated (25%) or undifferentiated (66%) tumours, so the poor expression of catenin-bin the membrane, as well as nuclear localization, is associated with a poor prognosis, regardless of the presence of other prognostic markers except that of tumour differentiation. The analysis of this characteristic may be helpful as a marker to classify the subtype of thyroid neoplasia and predict its evolution. Furthermore, as has been reviewed, it has been seen that the expression of catenin-bIt is decreased in 66% of adenomas and 100% of TCs. This decrease in expression correlates with increased aggressiveness and tumour progression towards undifferentiated stages. Mutations of these molecules occur in 61% of malignant thyroid neoplasms. (Table 1) (Li, Ying et al. 2024).

The findings of the changes that occur concerning Galectin 3 are fascinating. It is well known that the normal thyrocyte does not express the adhesion molecules CD44v6 or Galectin 3. However, these molecules are invariably present in thyroid proliferation. It seems, therefore, that the expression of Galectin 3 is a trait that guides quite specifically towards the malignancy of the lesion., although some authors have also confirmed its expression in inflammatory foci of normal thyroid tissue. Galectin-3 plays an essential role in intercellular adhesion and cell-matrix interaction. The expression of this protein in neoplastic cells is cytoplasmic. Even though its expression can be detected in some adenomas, the intensity is different (Yun and Cohen 2024)

since it has been seen that its expression is increased in FC and even more intensely in PC. Furthermore, in PC, there is a direct relationship between the number of metastases and their level of expression, although this is lower in metastatic nodes than in primary tumours. Lack of CD44 expressionIN6 is associated with a worse evolution of TC, especially in CP. Furthermore, the lack of CD44 expression has been correlated with several poor prognostic factors, such as age over 60 years, presence of distant metastases and advanced TMN, as well as tumour recurrence and cancer-related mortality. However, there is controversy in this regard since other authors relate the expression of CD44 with the worse prognosis of thyroid tumours (Nabata, Lim, et al. 2024).

Angiogenic factors and growth factors

CT thyrocytes produce the angiogenic factor VEGF*(Vascular endothelial growth factor)*. It seems that immunohistochemical staining of thyroid tissue to detect the presence of VEGF may be a good prognostic marker. Co of the invasion and metastasis capacity of differentiated carcinomas. Increased expression is associated with more aggressive disease patterns. Some authors have even correlated VEGF expression with tumour undifferentiation. Other authors have not found an increase in VEGF expression in lymph nodes and lung metastases compared to the primary tumour. This marker can probably predict papillary tumours that have a greater tendency to evolve unfavourably due to an increased risk of developing metastasis (Table 1) (Saeed-Vafa, Chatzopoulos, et al. 2024).

Another growth factor, EGF*(Epidermal growth factor)*, In addition to promoting cell proliferation in the thyroid, also acts by inhibiting specific thyroid functions such as iodine transport and its organization, as well as the synthesis of peroxidase and thyroglobulin. That is, it promotes the proliferation of the thyroid cell but not its differentiation. For this reason, EGF is attributed to a role in tumour growth. It interacts typically with receptors on the cell membrane, and the ligand-receptor complex is subsequently internalized to present a second action in the nucleus. It is known that TGFa*(Tumour growth factor* a*)* also interacts with the EGF receptor (EGF-R), which contributes to the stimulation of proliferative action. The expression in the nucleus of EGF and EGF-R is a feature that is observed in both adenoma and CF. This expression has also been detected in the thyroid tissue of patients with Graves' Disease. Surprisingly, EGF expression decreases in the nucleus of CP cells, although it is present in the cytoplasm (Mu, Zhang et al. 2024).

Loss of heterozygosity

There is a particular relationship between the frequency of loss of heterozygosity and the prognosis of thyroid carcinoma. Thus, it has been seen that it is more frequent in CF than in CP, and both are surpassed by IC since a loss of heterozygosity is found in 19p in up to 36% of cases. In IC, there are frequently localized losses on the short arm of chromosome 16, which would indicate the probable absence of a suppressor gene in this location. This observation is supported by the fact that it has been seen that IC cell lines frequently present losses of 16p concerning differentiated carcinoma cell lines, which suggests the existence of some gene in this location that may be associated with the transformation from well-differentiated to undifferentiated carcinoma (Deng, Cheng, et al. 2024).

Conclusion

Current methods for diagnosing thyroid neoplasms have advanced significantly in recent years. However, currently, they cannot predict, in many cases, the precise clinical evolution nor indicate the most appropriate therapy for each neoplasm, or they are incapable. To reveal the ability of the tumour to develop local or distant metastases. The

cytological study cannot discriminate with a consistent degree of certainty between the benignity or malignancy of some neoplasms. It is expected that the clinical application of advances in molecular biology will provide, in the not-too-distant future, knowledge and tools that will allow a qualitative leap in the diagnosis and treatment of thyroid neoplasms and thereby overcome current limitations, both in the field of diagnosis and treatment. There is still a long way to go, knowing that every new advance answers one question but asks many new ones. However, modern technologies are emerging that offer new perspectives in the classical management of thyroid neoplasms, which will undoubtedly benefit the clinical management of patients affected by this disease.

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