Parathyroid Tumors

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Parathyroid tumors, and the related Primary hyperparathyroidism (PHPT), manifest primarily as a sporadic single-gland disease in over 90% of cases, while only about 1 in 10 cases are hereditary familial forms, which can affect from 1 to 4 parathyroid. Inherited forms include both familial isolated parathyroid tumors and four autosomal dominant syndromic forms, in which the parathyroid neoplasms are associated with other endocrine and non-endocrine abnormalities.

Keywords: parathyroid tumors ; gene mutations ; epigenetic signatures

1. Parathyroid Tumors

The parathyroids are four small endocrine glands located in the neck behind the thyroid. They are the “endocrine controllers” of calcium homeostasis that continuously monitor and regulate serum calcium levels through the synthesis and release of parathyroid hormone (PTH). Primary hyperparathyroidism (PHPT), due to a persistent PTH hypersecretion independent from serum calcium levels, is a pathological idiopathic condition indicative of the presence of hyperactive/hypercellular gland(s) (parathyroid hyperplasia) or parathyroid tumors. PHPT is caused by multiple hyperplastic parathyroids in about 15% of cases, and by parathyroid tumors in approximately 85% of cases[1]. Parathyroid tumors are rare endocrine neoplasms affecting 0.1–0.3% of the general population , comprising slow-growing benign PTH-secreting adenomas in almost 100% of cases, atypical parathyroid adenomas in about 1.2–1.3% of cases[2], and extremely rare malignant carcinoma in less than 1% of cases[3] . Conversely to parathyroid adenomas (PAs), parathyroid carcinomas (PCs) show signs of local invasion and/or distant metastases and are characterized by hyperproduction of massive amounts of PTH (up to about 100-fold higher than that of adenomas) and a severe, commonly untreatable, hypercalcemia that accounts for death in a majority of cases. Atypical parathyroid adenomas (aPAs) are a group of an intermediate form of parathyroid cancer, characterized by specific atypical histological features (i.e., solid growth pattern, fibrous bands, and cellular atypia) and with an uncertain malignant potential, which differs from malignant PCs mainly because of the absence of evident signs of local invasion and metastases[2] .

Parathyroid tumors, and the related PHPT, manifest primarily as a sporadic single-gland disease in over 90% of cases, while only about 1 in 10 cases are hereditary familial forms, which can affect from 1 to 4 parathyroids[4] (**Table 1**). Inherited forms include both familial isolated parathyroid tumors and four autosomal dominant syndromic forms, in which the parathyroid neoplasms are associated with other endocrine and non-endocrine abnormalities.

Table 1. Summary of main genetic, epigenetic and molecular signatures associated with different types of sporadic and inherited parathyroid tumors.

Disease	Mean Age of Onset	Tumor Presentation	Genetic Signature(s)	Molecular Features	Epigenetic Signatures
1. Sporadic parathyroid tumors					

Disease	Mean Age of Onset	Tumor Presentation	Genetic Signature(s)	Molecular Features	Epigenetic Signatures
Sporadic isolated parathyroid adenoma	Commonly in the sixth decade of life.	Single-gland adenoma.	Somatic biallelic inactivation of the *MEN1* tumor suppressor gene in 20–40% of cases. p15-q13 pericentromeric inversion in chromosome 11 in about 5% of cases. Inactivating mutation of the *CDC73* tumor suppressor gene in 2–4% of cases. Rare somatic and germinal inactivating mutations of the *CDKN1A*, *CDKN1B*, *CDKN2B* and *CDKN2C* genes. Activating p.Tyr641Asp missense mutation of the *EZH2* gene in few cases.	Deregulation/loss of expression of menin protein in 20–40% of cases. Over-expression of the cyclin D1 protein in 30–40% of cases. Down-regulation of parafibromin expression in less than 5% of cases.	Hypermethylation (and silencing) of promoters of *RASSF1A*, *APC*, *SFRP1*, *SFRP2, SFRP4, CDKN2B*, *CDKN2A*, *WNT1* and *PAX1* genes.
Sporadic isolated parathyroid carcinoma	Commonly in the fifth decade of life.	Single-gland carcinoma.	Somatic biallelic inactivating mutations/loss of the *CDC73* tumor suppressor gene in 70–100% of cases. Amplification of the genomic region containing the *CCDN1* gene in about 30% of cases. Somatic and germinal inactivating mutations of the *PRUNE2* gene.	Deregulation/loss of expression of parafibromin protein in 70–100% of cases. Complete absence of nuclear staining for parafibromin. Over-expression of the cyclin D1 protein in about 90% of cases.	Hypermethylation (and silencing) of promoters of *RASSF1A*, *SFRP1*, *SFRP2, SFRP4, CDKN2B*, *CDKN2A*, *WNT1*, *SOCS3*, *PYCARD*, *HOXC11*, *GATA4* and *HIC1* genes. Down-regulation of miR-296, miR-126-5p, miR-26b and miR-30b. Up-regulation of miR-222, miR-503 and miR-517c. Down-regulation of lncRNA GLIS2-AS1. Up-regulation of lncRNA PVT1 and lncRNA BC200.
2. Inherited isolated parathyroid tumors					
Familial isolated hyperparathyroidism (FIHP)	Variable, but usually about two decades before the sporadic form of parathyroid cancer.	Multiple-gland tumors.	The specific genetic cause of FIHP has not yet been clearly identified. Inactivating mutations of the *MEN1* and the *CDC73* tumors suppressor genes and of the *CaSR* gene, as well as activating mutations of the *GCM2* gene, have been reported in some cases.	Loss of menin and parafibromin has been seen in a percentage of FIHP pedigrees.	Not reported.
3. Inherited syndromic parathyroid tumors					

Disease	Mean Age of Onset	Tumor Presentation	Genetic Signature(s)	Molecular Features	Epigenetic Signatures
Multiple Endocrine Neoplasia Type 1 (MEN1)	**During the third decade of life.**	**Multiple-gland adenomas (all the four parathyroids are affected during life). Extremely rare cases of aPAs and PCs.**	**Germinal heterozygote inactivating mutation, associated with somatic inactivation/loss of the second copy of the *MEN1* tumor suppressor gene, mainly by LOH, or, rarely, by intragenic mutations.**	**Loss of wild type menin expression. Loss of nuclear localization of the menin protein.**	**Increased activity of DNMT1. Increased expression of miR-24-1 in PAs without *MEN1* LOH.**
Multiple Endocrine Neoplasia Type 2A (MEN2A)	**During the fourth decade of life.**	**Single-gland or multiple-gland adenomas (1 to 4 glands can be affected during life). Only two cases of metastatic PCs have been reported.**	**Germinal heterozygote dominant activating mutations in exons 10 and 11 of the *RET* proto-oncogene (p.Cys634Arg missense mutation in 85% of cases).**	**Homodimerization of the RET receptor in absence of ligand. Constitutively active RET-mediated signal transduction.**	**Not reported.**
Multiple Endocrine Neoplasia Type 4 (MEN4)	**During the fourth decade of life.**	**Multiple-gland adenomas (all the four parathyroids are affected during life). No cases of aPAs and PCs have been reported.**	**Germinal heterozygote loss-of-function mutations of the *CDKN1B* tumor suppressor gene.**	**Reduced/absent nuclear expression of the $p27^{Kip1}$ cell cycle inhibitor protein.**	**Not reported.**
Hyperparathyroidism-Jaw Tumor syndrome (HPT-JT)	**Between the third and fourth decades of life.**	**Single- or multiple-gland adenomas in about 85% of cases; malignant carcinomas in up to 15% of cases.**	**Germinal heterozygote inactivating mutation with somatic biallelic inactivation/loss of the *CDC73* tumor suppressor gene.**	**Loss of parafibromin expression. Complete absence of nuclear staining for parafibromin.**	**Positive expression of the histone H1.2. Loss of the H2BK120ub1 histone modification.**

Parathyroid tumors present a great heterogeneity in their genetic background and molecular features, for both inherited and sporadic forms. Unfortunately, no specific histological characteristics allow pre-operative distinction among PAs, aPAs, and PCs. It is therefore of vital importance to increase our knowledge of genetic, epigenetic, and molecular signatures, which characterize different parathyroid tumor subtypes and drive different tumorigeneses, to identify potential diagnostic biomarkers able to distinguish among different parathyroid neoplastic types, as well as to provide novel therapeutic targets and strategies for these rare neoplasms, which are still a clinical and therapeutic challenge.

2. Inherited Syndromic Parathyroid Tumors

Inherited syndromic forms of parathyroid tumors include MEN1, Multiple Endocrine Neoplasia type 2A (MEN2A), Multiple Endocrine Neoplasia type 4 (MEN4), and HPT-JT syndrome.

It has recently been shown that loss of menin in MEN1-related PAs is associated with an increased activity of the DNA (cytosine-5)-methyltransferase 1 (DNMT1), an enzyme responsible for methylation of cytosine residues of the CpG islands of DNA. Addition of methyl groups to CpG dinucleotides in gene promoters results in silencing gene expression.

Hypermethylation of promoters of tumor suppressor genes, following menin loss, was demonstrated to be a common pro-oncogenic epigenetic change in MEN1 pancreatic neuroendocrine tumors[5] , and a similar mechanism can be suspected also in MEN1 loss-driven parathyroid tumorigenesis, both for the syndromic and the sporadic forms.

CDC73 is a tumor suppressor gene that encodes a nuclear protein, named parafibromin, a component of the human PAF1 complex, which controls gene transcription by interacting with the subunit A of the RNA polymerase II, with the SUV39H1 histone methyltransferase complex (promoting H3K4 and H3K79 methylations), and with the RNF20/RNF40 ubiquitine ligase complex (promoting monoubiquitination of histone H2B at the lysine residue K120; H2BK120ub1). Moreover, parafibromin activates Wnt signaling by directly interacting with β-catenin and suppresses tumor growth via the down-regulation of cyclin D1 expression, inhibiting the G1 to S phase transition of the cell cycle and inducing apoptosis of tumor cell.

PAF1 complex interacts with the histone H1.2. Normally, H1.2 inhibits transcription of growth suppressive genes via modulation of chromatin structure [6]. In about half of parathyroid tumors bearing a CDC73 mutation, and showing loss of parafibromin, a positive expression of H1.2 was found in more than 60% of cells, and the H1.2-regulated transcripts resulted as up-regulated (over 2-fold the mean expression values of normal parathyroid tissue) in 80% of CDC73 -mutated parathyroid tumors, including HPT-JT PAs and PCs, FIHP parathyroid tumors and sporadic PCs, suggesting an increased H1.2-driven inhibition of cell growth suppressive genes and subsequent promotion of cell proliferation as a common pro-oncogenic mechanism in CDC73 -mutated parathyroid cells.

3. Sporadic Parathyroid Tumors

Sporadic parathyroid tumors occur as single-gland disease in almost all cases, usually by the age of 50 years, with a female/male ratio of about 3:1 [5]. The etiology of non-inherited parathyroid tumors remains largely unclear; older age, female gender and previous exposure to neck irradiation are considered main risk factors [2][3]. Somatic and, more rarely, germinal mutations in specific genes have been identified as responsible for the pathogenesis of sporadic parathyroid tumors in variable percentages of cases and with different genetic signatures distinguishing PAs from PCs.

In sporadic parathyroid tumors bearing MEN1 or CDC73 mutations, the deregulation of DNA methylation mechanism and/or of histone modifications, derived by menin or parafibromin loss, substantially concurs to the tumorigenesis, the same way it happens in inherited forms of MEN1- and HPT-JT-related parathyroid tumors.

As for other human malignancies, the deregulation of epigenetic mechanisms can cooperate with genetic alterations in parathyroid tumor development and growth, driving the tumor phenotype, and it is strongly suspected to be a main factor responsible for the wide heterogeneity in biological and clinical presentation of different neoplasms. However, as opposed to other human cancers that have shown a genome-wide DNA hypomethylation of the intragenic regions, parathyroid tumors do not appear to be affected by changes in global DNA methylation pattern compared to normal tissue [7]. On the contrary, the site-specific methylation of CpG dinucleotides, and the subsequent silencing of the regulated gene, in the promoters of tumor suppressor genes and genes known to be related to regulation of parathyroid pathophysiology, cell cycle progression and Wnt signaling appear to be a pro-oncogenic factor in parathyroid tumors. Promoter hypermethylation/silencing of the Adenomatous Polyposis Coli (APC) and Ras-association Domain Family Member 1A (RASSF1A) tumor suppressor genes have been demonstrated to be a common epigenetic change in parathyroid tumors [7][8][9].

A tissue microarray analysis of lncRNA expression patterns, associated with immunohistochemical evaluation of tumor features in normal, hyperplastic, and benign and malignant neoplastic parathyroid samples, found the expression of lncRNAs ROR, HOTAIR and MALAT1 in all four of the parathyroid tissues analyzed, including both healthy and tumoral glands[10]. Only the lncRNA ROR showed a decreasing expression during the tumor progression from PAs to PCs, suggesting that this lncRNA may act as a tumor suppressor in parathyroid tumors.

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