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Review

Parathyroid Carcinoma: Update on Pathogenesis and Therapy

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Abstract: Parathyroid carcinoma (PC) is a very rare endocrine cancer with aggressive behavior, a high metastatic potential, and a poor prognosis. Surgical resection of affected gland(s) and other involved structures is the elective therapy. Pre-operative and intra-operative differential diagnosis with benign parathyroid adenoma remains a challenge. The lack of a clear pre-operative diagnosis does not allow one, in many cases, to choose the correct surgical approach to malignant PC, increasing persistence, the recurrence rate, and the risk of metastases. An initial wrong diagnosis of parathyroid adenoma, with a minimally invasive parathyroidectomy, is associated with over 50% occurrence of metastases after surgery. Genetic testing could help in identifying patients at risk of congenital PC (i.e., *CDC73* gene) and in driving the choice of neck surgery extension. Targeted effective treatments, other than surgery, for advanced and metastatic PC are needed. The pathogenesis of malignant parathyroid carcinogenesis is still largely unknown. In the last few years, advanced molecular techniques allowed researchers to identify various genetic abnormalities and epigenetic features characterizing PC, which could be crucial for selecting molecular targets and developing novel targeted therapeutic agents. We reviewed current findings in PC genetics, epigenetics, and proteomics and state-of-the-art therapies.

Keywords: parathyroid carcinoma; *CDC73* gene; gene mutation; epigenetic alterations; molecular targeted therapy

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1. Introduction

Parathyroid carcinoma (PC) is an extremely rare endocrine malignancy of the parathyroid glands, representing about 1% of all parathyroid tumors and one of the rarest causes of primary hyperparathyroidism (PHPT), and generally presenting more severe symptomatic hypercalcemia than its benign counterparts (hyperplasia and adenoma), with marked skeletal and renal complications, including osteoporosis, fragility fracture, osteitis fibrosa cystica, and nephrolithiasis [1]. This tumor has aggressive behavior and high metastatic potential. Patients with PC show a poor prognosis, with an overall survival rate of 85% and 49%, respectively, at 5 and 10 years after diagnosis, due to commonly unmanageable, severe, and drug-refractory hypercalcemia [2]. Tumor stage, adjacent tissue invasion, and malignant local and distant metastases, at the time of first diagnosis, still represent critical prognostic factors.

The majority of PC occur as sporadic cancer; only occasionally, it is part of congenital syndromic and non-syndromic endocrine diseases, such as hyperparathyroidism–jaw tumor syndrome (HPT-JT) or isolated familial hyperparathyroidism (FIPH), and, in extremely rare cases, multiple endocrine neoplasia type 1 and type 2A (MEN1 and MEN2A, respectively).

The diagnosis of PC is still a challenge. Some biochemical, clinical, and radiological features may help in discriminating PC by benign adenoma, in some cases. Currently, the diagnosis of malignant carcinoma principally derives from a combination of operative findings by surgeons, such as vascular invasion, invasion of the recurrent nerve or esophageal wall, thick adherent capsule, the presence of lymph node metastases, a tumor mass over 2 g, and the presence of four or more histological characteristics of malignancy in a tumor sample assessed by pathologists, such as intra-tumoral bands, signs of necrosis, the presence of small cells with a large nucleus (macronuclei) and a reduced cytoplasm/nucleus ratio, diffuse cellular atypia, the presence of more than 6 mitoses per 10 high-power field, signs of capsular disruption, and invasion of adjacent tissue [3]. However, even with the presence of such features, a clear diagnosis of PC remains difficult, and it is operator-dependent. The loss of nuclear parafibromin immunostaining in the tumor specimen may further confirm the intra-operative and histological suspicion of PC.

Recently, a high expression of cancer-derived immunoglobulin G (CIgG) was found in PC samples, being significantly higher in PC patients than in patients with parathyroid adenoma (PA) or hyperplasia ($p < 0.001$) and borderline significantly higher in recurrent or metastatic lesions of PC compared with the primary tumor ($p = 0.055$) [4], suggesting the possibility to use this parameter as a possible adjunctive biomarker of PC diagnosis and for the prediction of disease relapse in clinical practice.

PC specimens were also shown to have a remarkable loss of nuclear staining of the Yes-associated protein 1 (YAP1) [5], an increased cytoplasmic expression of the Filamin A (FLNA) protein [6], and a reduced number of cells positive for the expression of the T-box transcription factor 1 (TBX1) [7], with respect to PA and/or normal parathyroids. However, these molecular features need to be confirmed before they could be used as markers to distinguish PC from benign PA.

An additional challenge is to distinguish between the recurrence of PC after surgery and the possible occurrence of post-operative parathyromatosis, an extremely rare cause of recurrent primary hyperparathyroidism, consisting of the formation of several nodules of hyperfunctioning parathyroid tissue in the neck and mediastinum due to the incidental seeding of benign parathyroid cells in neck soft tissue after surgical procedures. The parathyromatosis lesion(s) do not reflect the histological and genetic characteristics of the primary PC, and they are usually located in different anatomic sites with respect to PC recurrence and/or metastases.

Surgical resection of affected gland(s) and other involved tissue is still the elective therapy for PC, but it has limited efficacy in the case of advanced and metastatic cancer. Therefore, the identification of genetic and epigenetic drivers of parathyroid carcinogenesis and tumor malignant aggressiveness, as well as of pathways specifically deregulated in PC tumor cells, is fundamental to selecting potential molecular targets for the development of targeted treatments.

In this review, current findings in PC genetics, epigenetics, and proteomics and state-of-the-art therapies were reviewed.

2. Pathogenesis of Parathyroid Carcinoma

The etiology of PC remains still to be fully elucidated, and it is not yet known whether PC arises de novo or as a malignant progression of parathyroid hyperplasia and adenoma. The rarity of the disease and the lack of studies have made it impossible to solve this issue so far. Interestingly, in patients with chronic kidney disease-derived secondary hyperparathyroidism, a frequent cause of parathyroid hyperplasia/adenoma, including those with end-stage renal disease who commonly experience multiple parathyroid adenomas, the malignant transformation of the disease has never been reported.

The contemporary presence, in some patients, of PC, PA, and/or atypical parathyroid adenoma (aPA) and also the occurrence of different parathyroid phenotypes in members of the same family, without any genotype–phenotype correlation, in the inherited forms of PC make the elucidation of the specific etiological bases of PC very complex.

A germline genetic background has been established for the congenital PC forms, often in association with somatic additional genetic abnormalities in tumor cells. The occurrence of various somatic genetic alterations has been described in subsets of sporadic PC cases, presenting a variable spectrum among patients.

Recently, specific epigenetic alterations, including the hypermethylation of gene promoters, modification of the chromatin structure, and altered expression of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have been associated with PC and are suspected to have a role in tumor suppression inactivation and in the induction/progression of carcinogenesis.

2.1. Genetics of Parathyroid Carcinoma

2.1.1. *CDC73* Gene

Biallelic loss-of-function mutations of the *CDC73* tumor suppressor gene are the most common genetic defect of sporadic and congenital PC forms but are found in less than 5% of PAs, suggesting that loss of tumor suppressor activity of the encoded protein can confer the mutated cell aggressive growth potential and malignant behavior and that the identification of *CDC73* mutations in tumor cells can be a molecular marker to distinguish between malignant and benign parathyroid neoplasms.

Somatic inactivation or the loss of at least one *CDC73* allele is found in 9–100% of sporadic PC, depending on the analyzed series [1], and homozygote *CDC73* inactivation/loss is reported in 9–70% of cases [8]. In the inherited PC forms, heterozygote germline inactivating mutations of *CDC73* are detected in 50–75% of HPT-JT pedigrees and in about 8% of FIPH families [9]. In these hereditary PCs, *CDC73* mutations consist of a "first germline hit", inherited by the affected parent and present in all cells, and a somatic inactivation/loss of the second allele in the tumor-originating parathyroid cell (in most cases due to a large deletion at the 1q31.2 locus).

The presence of a germline mutation of the *CDC73* gene not only predisposed to the development of malignant PC but was associated with the risk of disease recurrence after parathyroidectomy [10].

Germline and somatic mutations of the *CDC73* gene identified, to date, in the sporadic form of PC and in the context of HPT-JT syndrome and FIPH are summarized in Table 1, Table 2, and Table 3, respectively.

Table 1. Germline and somatic mutations of the *CDC73* gene identified in sporadic parathyroid carcinoma.

***CDC73* Mutation (cDNA Reference Sequence GenBank Accession Number NM_024529.4)**	**Gene Site**	**Type of Mutation**	**Predicted Effect on the Parafibromin**	**Reference**
Germline mutations				
c.12-31dup	Exon 1	Frameshift/premature stop codon	p.Tyr11CysfsX17	[11]
c.30delG	Exon 1	Frameshift/premature stop codon	p.Gln10HisfsX11	[12,13]
c.32delA	Exon 1	Frameshift/premature stop codon	p.Tyr11SerfsX10	[12]
c.40delC	Exon 1	Frameshift/premature stop codon	p.Gln14ArgfsX7	[11]
c.40C>T	Exon 1	Nonsense	p.Gln14X	[14]
c.70G>T	Exon 1	Nonsense	p.Glu24X	[15]
c.78delC	Exon 1	Frameshift variant	p.Ile26fs	[16]
c.96G>A	Exon 1	Nonsense	p.Trp32X	[14]
c.127_128insC	Exon 1	Frameshift/premature stop codon	p.Trp43SerfsX23	[17]
c.126_131+9delinsCT	Intron 1	Splicing site	Not reported	[18]
c.176C>T	Exon 2	Missense	p.Ser59Phe	[19]
c.226C>T	Exon 2	Nonsense	p.Arg76X	[20,21]
c.260_261delGA	Exon 3	Frameshift/premature stop codon	p.Arg87Lysfs2X	[14,22]
c.271C>T	Exon 3	Frameshift/premature stop codon	p.Arg91X	[23]
c.307+1G>A	Intron 3	Splicing site	Not reported	[24]
c.343G>T	Exon 4	Nonsense	p.Glu115X	[25,26]

Table 1. *Cont.*

***CDC73* Mutation (cDNA Reference Sequence GenBank Accession Number NM_024529.4)**	**Gene Site**	**Type of Mutation**	**Predicted Effect on the Parafibromin**	**Reference**
c.355C>T	Exon 4	Nonsense	p.Gln119X	[16]
c.356delA	Exon 4	Frameshift/premature stop codon	p.Gln119ArgfsX14	[12,13]
c.375dupA	Exon 5	Frameshift/premature stop codon	p.Glu130X	[27]
Not reported	Exon 5	Frameshift/premature stop codon	p.Lys125_Arg126fs	[13]
c.376C>T	Exon 5	Nonsense	p.Arg126X	[28]
c.415C>T	Exon 5	Nonsense	p.Arg139X	[26,29,30]
c.423+1G>A	Intron 5	Splicing site	Not reported	[31]
c.496C>T	Exon 6	Nonsense	p.Gln166X	[16,23,32]
c.539_544insA	Exon 7	Frameshift/premature stop codon	p.Ile182AsnfsX10	[12]
c.544dup	Exon 7	Frameshift/premature stop codon	p.Ile182AsnfsX11	[33]
c.571delG	Exon 7	Frameshift/premature stop codon	p.Ala191LeufsX11	[14]
c.580A>T	Exon 7	Nonsense	p.Arg194X	[34]
c.626_629delAACA	Exon 7	Frameshift/premature stop codon	p.Lys209Arg.fs217X	[14,22]
c.664C>T	Exon 7	Nonsense	p.Arg222X	[13,14,17,27,35]
c.681insAG	Exon 7	Frameshift	p.Arg227_Glu228fs	[13]
c.685A>T	Exon 7	Nonsense	p.Arg229X	[23]
c.685_688delAGAG	Exon 7	Frameshift/premature stop codon	p.Arg229TyrfsX27	[14,36]
c.687_688dupAG	Exon 7	Frameshift/premature stop codon	p.Arg227Lysfs31X	[27,37]
c.687_688delAG	Exon 7	Frameshift/premature stop codon	p.Arg229SerfsX37	[14,22,28,38]
c.692_693insT	Exon 7	Frameshift/premature stop codon	p.Trp231CysfsX36	[19]
c.700C>T	Exon 7	Nonsense	p.Arg234X	[26,39]
c.728+2T>G	Intron 7	Splicing site	Not reported	[36]
c.1242delA	Exon 14	Frameshift	Not reported	[31]
Deletion of exon 1	Exon 1	Gross deletion	Not reported	[40]
Deletion of exon 1	Exon 1	Gross deletion	Not reported	[33]
Deletion of exons 1–13	Exons 1–13	Gross deletion	Not reported	[41]
Deletion of exons 4–10	Exons 4–10	Gross deletion	Not reported	[42]
Deletion of exon 17	Exons 17	Gross deletion	Not reported	[23]
Deletion of exon 17	Exons 17	Gross deletion	Not reported	[43]
Deletion of the entire *CDC73* gene	Exons 1–17	Gross deletion	Not reported	[36]
		Somatic mutations		
c.13C>T	Exon 1	Missense	p.Leu5Phe	[38]
c.13_30del18	Exon 1	In-frame deletion	p.Leu5_Gln10del	[44]
c.16delA	Exon 1	Frameshift/premature stop codon	p.Ser6AlafsX15	[13]
c.23_26delinsTGCG>GTG	Exon 1	Frameshift/premature stop codon	p.Leu8ArgfsX12	[17,27]
c.25C>T	Exon 1	Nonsense	p.Arg9X	[26,39]
c.32delA	Exon 1	Frameshift/premature stop codon	p.Tyr11SerfsX10	[13]
c.39delC	Exon 1	Frameshift	p.Ile13fs	[13]
c.40delC	Exon 1	Frameshift/premature stop codon	p.Gln14ArgfsX7	[27]
c.42delG	Exon 1	Frameshift/premature stop codon	p.Gln14fsX20	[38]
c.60delG	Exon 1	Frameshift/premature stop codon	p.Val20ValfsX6	[26]
c.64G>T	Exon 1	Nonsense	p.Gly22X	[26]
c.70G>T	Exon 1	Nonsense	p.Glu24X	[17,26,27,29]
c.82_85del4	Exon 1	Frameshift/premature stop codon	p.Gly28SerfsX8	[17,27]
c.85delG	Exon 1	Frameshift/premature stop codon	p.Glu29SerfsX8	[20,44]
c.85G>T	Exon 1	Nonsense	p.Glu29X	[13]
c.94insTA	Exon 1	Frameshift/premature stop codon	p.Tyr32fsX37	[38]
c.128G>A	Exon 1	Nonsense	p.Trp43X	[19]
c.142G>T	Exon 2	Nonsense	p.Glu48X	[13]
c.162C>G	Exon 2	Nonsense	p.Tyr54X	[13,27]

Table 1. *Cont.*

***CDC73* Mutation (cDNA Reference Sequence GenBank Accession Number NM_024529.4)**	**Gene Site**	**Type of Mutation**	**Predicted Effect on the Parafibromin**	**Reference**
c.165C>A	Exon 2	Nonsense	p.Tyr55X	[45]
c.165delC	Exon 2	Frameshift	p.Tyr55fs	[12,13,19]
c.182T>A	Exon 2	Nonsense	p.Leu61X	[26,29]
c.195insA	Exon 2	Frameshift/premature stop codon	p.Asn66LysfsX16	[39]
c.195insT	Exon 2	Frameshift/premature stop codon	p.Asn66X	[26,39]
c.197dupA	Exon 2	Frameshift/premature stop codon	p.Asn66X	[26]
c.248delT	Exon 3	Frameshift/premature stop codon	p.Ile83IlefsX26	[26]
c.284T>C	Exon 3	Missense	p.Leu95Pro	[12,13]
c.343G>T	Exon 4	Nonsense	p.Glu115X	[26]
c.415C>T	Exon 5	Nonsense	p.Arg139X	[26]
c.513-1delG	Intron 6	Splicing site	Not reported	[45]
c.520_523delTCTG	Exon 7	Frameshift/premature stop codon	p.Ser174LysfsX27	[21,30]
c.687_688delAG	Exon 7	Frameshift/premature stop codon	p.Arg229SerfsX37	[38]
c.700C>T	Exon 7	Nonsense	p.Arg234X	[26,46]
c.736delT	Exon 8	Frameshift/premature stop codon	p.Ser246ProfsX11	[17,27]
c.750delT	Exon 8	Frameshift/premature stop codon	p.Phe250LeufsX7	[17]
c.1230delC	Exon 14	Frameshift	p.Gln410fs	[13]
		Undetermined mutations *		
c.1A>T	Exon 1	Missense	p.Met1Leu	[47]
c.60_69del10	Exon 1	Frameshift/premature stop codon	p.Gly22X	[27]
Not reported	Exon 1	Frameshift/premature stop codon	p.Val25fs1X	[48]
c.76delA	Exon 1	Frameshift/premature stop codon	p.Ile26SerfsX11	[45]
Not reported	Exon 1	Frameshift/premature stop codon	p.Phe27fsX9	[48]
c.85G>T	Exon 1	Nonsense	p.Glu29X	[47,48]
c.96G>A	Exon 1	Nonsense	p.Trp32X	[2,47]
c.128G>A	Exon 1	Nonsense	p.Trp43X	[48]
c.131+1G>A	Intron 1	Splicing site	Not reported	[47]
Not reported	Exon 2	Nonsense	p.Arg52X	[48]
c.157G>T	Exon 2	Nonsense	p.Glu53X	[47]
c.162C>G	Exon 2	Nonsense	p.Tyr54X	[22,45,47]
c.164A>G	Exon 2	Missense	p.Tyr55Cys	[2]
c.165delC	Exon 2	Frameshift	p.Tyr55fs	[45]
Not reported	Exon 2	Nonsense	p.Tyr55X	[2]
c.237+1G>C	Intron 2	Splicing site	Not reported	[48]
c.271C>T	Exon 3	Frameshift/premature stop codon	p.Arg91X	[47,48]
c.415C>T	Exon 5	Nonsense	p.Arg139X	[36]
Not reported	Exon 7	Frameshift/premature stop codon	p.Ile182fsX20	[48]
c.664C>T	Exon 7	Nonsense	p.Arg222X	[22]
c.668delA	Exon 7	Frameshift/premature stop codon	p.Asp223ValfsX34	[36]
Not reported	Exon 7	Frameshift/premature stop codon	p.Val230fsX28	[48]
c.693_694dupG	Exon 7	Frameshift/premature stop codon	p.Arg232GlufsX35	[19]
c.700C>T	Exon 7	Nonsense	p.Arg234X	[27,47]
c.704delC	Exon 7	Frameshift/premature stop codon	p.Thr235LysfsX22	[36]
Not reported	Exon 14	Nonsense	p.Ser389X	[48]
c.1231delC	Exon 14	Frameshift/premature stop codon	p.Gln411ArgfsX17	[27]
Deletion of exon 1	Exon 1	Gross deletion	Not reported	[36]
Deletion of exons 2–10	Exons 2–10	Gross deletion	Not reported	[36]
Deletion of exon 17	Exon 17	Gross deletion	Not reported	[36]

* = heterozygote mutations found in the tumor tissue, but germline DNA was not tested. Mutations reported only in sporadic atypical parathyroid adenoma and/or benign parathyroid adenoma were not included in the table.

Table 2. Germline and somatic mutations of the *CDC73* gene identified in parathyroid carcinoma in the context of HPT-JT syndrome.

***CDC73* Mutation (cDNA Reference Sequence GenBank Accession Number NM_024529.4)**	**Gene Site**	**Type of Mutation**	**Predicted Effect on the Parafibromin**	**Reference**
Germline mutations				
c.-2insG	5′-UTR	Regulatory?	Not reported	[49]
c.-4_-11insG	5′-UTR	Regulatory?	Not reported	[50]
c.14_17dupTTAG	Exon 1	Frameshift/premature stop codon	p.ValfsX7	[51]
c.18_46del31	Exon 1	Frameshift/premature stop codon	p.Ser6ArgfsX50	[52]
c.76delA	Exon 1	Frameshift/premature stop codon	p.Ile26SerfsX11	[45,53]
c.96G>A	Exon 1	Nonsense	p.Trp32X	[54]
c.131+1delG	Intron 1	Splicing site	Not reported	[55]
c.165C>A	Exon 2	Nonsense	p.Tyr55X	[56]
c.165C>G	Exon 2	Nonsense	p.Tyr55X	[11]
c.191_192delT	Exon 2	Frameshift/premature stop codon	p.Leu64LeufsX44	[57]
c.226C>T	Exon 2	Nonsense	p.Arg76X	[58,59]
c.271C>T	Exon 3	Frameshift/premature stop codon	p.Arg91X	[36]
c.276delA	Exon 3	Frameshift/premature stop codon	p.Asp93IlefsX16	[49]
c.306_307+13del	Exon 3	Frameshift/premature stop codon	p.Ser103AsnfsX5	[11]
c.356delA	Exon 4	Frameshift/premature stop codon	p.Gln119ArgfsX14	[11]
c.358C>T	Exon 4	Nonsense	p.Arg120X	[60]
c.433_442delinsAGA	Exon 6	Frameshift/premature stop codon	p.Cys145ArgfsX55	[49,61]
c.668_669delAT/insG	Exon 7	Frameshift/premature stop codon	p.Asp223GlyfsX34	[62]
c.687_688dupAG	Exon 7	Frameshift/premature stop codon	p.Arg227Lysfs31X	[11,63]
c.700C>T	Exon 7	Nonsense	p.Arg234X	[53,64]
c.1346delG	Exon 15	Frameshift/premature stop codon	p.Gly449ValfsX30	[53]
c.1382delT	Exon 15	Frameshift/premature stop codon	p.Leu460LeufsX18	[65]
Deletion of exons 1–10	Exons 1–10	Gross deletion	Not reported	[66]
Deletion of exons 4–10	Exons 4–10	Gross deletion	Not reported	[50]
Somatic mutations				
c.70delG	Exon 1	Frameshift/premature stop codon	p.Glu24LysfsX2	Sriphrapradang 2014
c.686_689delGAGT	Exon 7	Frameshift/premature stop codon	p.Arg229AsnfsX27	[67]
Undetermined mutations *				
c.238-1G>A	Intron 2	Splicing site	Not reported	[44,68]

* = heterozygote mutations found in the tumor tissue, but germline DNA was not tested. Mutations reported only in HPT-JT-associated atypical parathyroid adenoma and/or benign parathyroid adenoma were not included in the table.

CDC73 encodes a nuclear ubiquitously expressed, evolutionarily conserved protein, parafibromin, an essential component of Polymerase-associated Factor 1 (PAF1), involved in the regulation of the elongation of gene transcripts and mRNA 3′-end processing, gene expression, chromosome stability, cell cycle regulation, apoptosis, and nuclear transduction of the Wnt canonical signaling. Truncating mutations (nonsense and frameshift variants), which represent more than 80% of *CDC73* pathogenic variants in PCs, prevents parafibromin from the nuclear localization and, thus, from the exertion of its biological functions, conferring to the mutated cell a growth advantage and, thus, being responsible for PC carcinogenesis.

Table 3. Germline and somatic mutations of the *CDC73* gene identified in parathyroid carcinoma in the context of FIHP.

***CDC73* Mutation (cDNA Reference Sequence GenBank Accession Number NM_024529.4)**	**Gene Site**	**Type of Mutation**	**Predicted Effect on the Parafibromin**	**Reference**
Germline mutations				
c.131+1G>A	Intron 1	Splicing site	Not reported	[62]
c.191T>C	Exon 2	Missense	p.Leu64Pro	[45]
c.307+1G>A	Intron 3	Splicing site	Not reported	[24]
c.548delC	Exon 7	Frameshift	p.Ser195fs	[69]

Mutations reported only in FIHP-associated atypical parathyroid adenoma and/or benign parathyroid adenoma were not included in the table.

In addition to gene mutations, epigenetic silencing of the *CDC73* gene, by hypermethylation of the 5′UTR promoter region, has been described as a somatic event in PC [70].

The absence of nuclear parafibromin immunohistochemical staining in tumor specimens is a common hallmark in PC, with a sensitivity and a specificity of 75–90% and over 90%, respectively, which could be used as a marker, together with other histological features, to distinguish PC and PA [8], and it appears to also be a promising predictor of PC prognosis, in particular as an indicator of a higher risk of cancer recurrence and metastasis, and of mortality [71].

2.1.2. *CCND1* Gene

The *CCND1* gene encodes cyclin D1, a positive regulator of the cell cycle, through the promotion of G1-S phase transition via the activation of the cyclin-dependent kinases CDK4/CDK6. Cyclin D1 has also a role in chromosome stability, whose deregulation could be involved in PC tumorigenesis. The over-expression of cyclin D1 has been reported in up to 90% of PCs [72].

A somatic heterozygote 11p15-q13 pericentromeric inversion, positioning the 5′-regulatory element of the parathyroid hormone (PTH) gene upstream to the *CCND1* gene, was found in two unrelated cases of sporadic PA, but not in PC. The transgenic mouse model mimicking this chromosomal rearrangement at the *Ccnd1* locus developed hyperplastic parathyroid glands, chronic PHPT with hypercalcemia, and bone abnormalities but not PC [73]. These data, together with the fact that cyclin D1 up-regulation is reported in 20–40% of PAs [9], seem to indicate that the over-expression of cyclin D1 alone may not be sufficient to drive malignant carcinogenesis, and the presence of other concurrent genetic or epigenetic alterations is suspected to synergize in leading to the malignant phenotype.

A whole-genome study identified an alteration of the *CCND1* locus in 29% of the analyzed sporadic PC cases, showing that it is due to the amplification of the gene [13]. Zhao et al. [73] showed that the amplification of the *CCND1* gene was more prevalent in PCs than in adenomas (71% vs. 21%), suggesting that the gain of copy number of the *CCND1* gene is the principal mechanism of cyclin D1 over-expression in PCs. Interestingly, 80% of *CCND1*-amplified PCs and cases with somatic inactivation/loss of the *CDC73* gene were mutually exclusive [73], suggesting that *CCND1* amplification and *CDC73* inactivation represent two alternative mechanisms leading to the over-expression of cyclin D1 and the subsequent enhancement of cell growth.

2.1.3. *PRUNE2* Gene

In 2015, germline and somatic mutations of the *PRUNE2* tumor suppressor gene were identified, for the first time, as associated with PC [12]. The whole-exome sequencing analysis of 8 unrelated sporadic PCs identified three mutations in exon 8 of the *PRUNE2* gene (18% of the analyzed cases) but not in all 40 screened PAs [12]. The selective sequencing of exon 8 in a validation group of 13 PC samples found two additional heterozygote somatic missense mutations in 2 PC cases (15.4%) [12].

A heterozygote germline missense mutation (p.Val452Met) was identified in one PC from the discovery group, associated with somatic LOH of the *PRUNE2* locus on chromosome 9, while two heterozygote somatic missense mutations (p.Ser450Asn and p.Gly455Asp) were found in two PCs from the validation group, with all these three variants in the absence of a *CDC73* mutation [12]. In the discovery group, two heterozygote somatic nonsense mutations (p.Glu474X and p.Glu537X) were identified in a single PC sample, presumably inactivating both the alleles of the *PRUNE2* gene, and in the presence of a somatic heterozygote mutation of the *CDC73* gene but no LOH of the gene. These two nonsense mutations and the p.Val452Met variant were found, respectively, at the somatic level in one PC sample and in the germline in one PC case by another whole-exome sequencing study [13], suggesting that they could be recurrent mutations involved in the development of sporadic PCs. The same study [13] also identified one novel germline missense variant (p.Glu2570Ala) in one PC case.

The *PRUNE2* gene encodes the homonym protein that exerts various biological functions, including the suppression of Ras homolog family member A activity, which results in reduced stress fiber formation and the suppression of oncogenic cellular transformation. Therefore, the inactivation/loss of this protein could exert a role in driving parathyroid malignant carcinogenesis and tumor progression, presumably by regulating the differentiation, survival, and aggressiveness of the tumor cells and their capacity to metastasize.

2.1.4. *MEN1* Gene

Germline loss-of-function mutations of the *MEN1* tumor suppressor gene are responsible for the development of the MEN1 syndrome, a rare inherited multiple endocrine tumor syndrome in which PHPT, caused by multiple parathyroid hyperplasia and/or adenoma, is the main and, in the majority of cases, the first occurring clinical manifestation. The occurrence of PC in MEN1 patients is extremely rare, and only less than 15 cases have been reported to date [9].

Two genomic profiling studies on sporadic advanced PC samples identified somatic alterations of the *MEN1* gene in 3/23 (13.0%) [19] and 6/16 (37.5%) [48] of the screened cases. A somatic mutation of the *MEN1* gene was found in the trachea metastasis from a sporadic PC, but not in the primary tumor [59].

2.1.5. Genes of the PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR signaling is a critical cell signal transduction pathway involved in the regulation of cell metabolism, growth, survival, and senescence, as well as in angiogenesis, whose constitutive activation is a common event in various human malignancies, including endocrine neoplasms, being responsible for increased cell proliferation, tumor cell metastatic spread, and tumor angiogenesis.

Somatic activating mutations in genes of the PI3K/AKT/mTOR pathway were identified in PC, such as the *PIK3CA* gene (p.Lys111Glu, p.Gly118Asp, p.Glu545Ala, p.Gln546Arg, p.Gln564Arg, and p.His1047Arg) [13,48,59], the *mTOR* gene (p.Leu1460Pro and p.Gln2524Leu) [13], and the *PTEN* gene (p.Asp107Tyr, p.Arg130Gln, and p.Phe90fsX1) [48,59].

One gene fusion and one copy number loss of the *PI3KCA* gene were found in PC samples by Hu et al. [47] through whole-genome sequencing. The same study found somatic mutations in the PI3K/AKT/mTOR pathway in 64.3% (9/14) of the analyzed PC samples from the discovery cohort samples, showing that they were positively correlated with cancer recurrence/metastasis [47]; the overall prevalence of somatic mutations in the PI3K/AKT/mTOR pathway was 78.3% (18/23) in the discovery and the extension cohorts [47].

Moreover, somatic inactivating mutations were found in the *TSC1* gene (p.Val25Met, p.Arg177X, and p.Arg228X) [2,59] and the *TSC2* gene (p.Ser9X and p.G654fsX2) [48], respectively encoding hamartin and tuberin, the two components of the hamartin–tuberin complex, which is responsible for the mTOR activity. When the hamartin–tuberin complex

is impaired, the mTOR increases, activating the PI3K/AKT/mTOR pathway and resulting in cell dysplasia, tumorigenesis, and angiogenesis [74].

Interestingly, Zhang et al. [75] demonstrated that inactivating *CDC73* mutations could confer parathyroid cancer cells a selective growth advantage by exerting, like mTOR, an inhibitory activity on the eukaryotic translation initiation factor 4E-binding protein (EIF4EBP) gene, encoding the homonym translation repressor, a known effector of mTOR signaling. Under physiological conditions and in its unphosphorylated form, EIF4EBP binds to the eucaryotic translation initiation protein (EIF4E) to inhibit mRNA-cap-dependent initiation of the translation of specific proteins, critical for cell proliferation and survival. The activation of the mTOR pathway leads the protein kinase mTOR to phosphorylate EIF4EBP and reduce its affinity and binding to EIF4E, inducing the translation of target proteins and promoting cell growth. Zhang et al. [75] showed that the promoter region of the *EIF4EBP* gene was a conserved target of parafibromin and that levels of the EIF4EBP protein were reduced in peripheral blood cells of patients with a *CDC73* germline heterozygote inactivating mutation. A haploinsufficiency of parafibromin, due to the presence of a heterozygote *CDC73* mutation, resulted in a reduction in/loss of *EIF4EBP* gene expression and the subsequent loss of its inhibition on the pro-translation activity of EIF4E, as it happens in the presence of a constitutively active mTOR kinase.

2.1.6. Genes of the Wnt Signaling Pathways

The Wnt signaling pathways are pleiotropic signal transduction pathways that regulate cell growth and survival and apoptosis through the modulation of gene expression. Constitutive or aberrant activation of Wnt signaling has been reported in human cancers. PC tumor samples were shown to have an increased cytoplasmatic accumulation of the non-phosphorylated active form of beta-catenin, the intracellular effector of the Wnt signal transduction in the Wnt canonical pathway, compared to the adjacent normal parathyroid tissues [76], suggesting that aberrant activation of canonical Wnt signaling could be a driver of parathyroid carcinogenesis.

Somatic inactivating genetic variants have been found in PC tissues in two genes involved in the regulation of Wnt signaling, the *APC* (p.Thr297Ile, p.Glu1284Lys, p.Ala1793Gly) [13,28] and the *RNF43* (p.Gly659fs) [13] genes, respectively encoding the APC protein, a main inhibitor of beta-catenin activation, and the RNF43 transmembrane ubiquitin-protein ligase, which negatively regulates both the canonical and the non-canonical Wnt pathways by selectively ubiquitinating frizzled receptors and promoting their proteasomal degradation. The inactivation of APC or RNF43 leads to aberrant activation of Wnt signaling and the subsequent transcription of target genes, such as the two regulators of the cell cycle S-phase, *c-MYC* and *CCND1*, resulting in the promotion of cell proliferation.

A heterozygote missense mutation, p.Arg380Gln, of uncertain clinical significance in the *WNT1* gene, encoding the homonym WNT1 ligand, the activator of the canonical Wnt pathway, was found in a PC sample also bearing a pathogenic mutation of the *CDC73* gene [28].

Strangely, a whole-exome study identified an inactivating missense mutation (p.Gln72X) of the *CTNNB1* oncogene, encoding beta-catenin 1, in two different formalin-fixed paraffin-embedded samples from the same PC patient of the primary tumor and the lung metastasis [2,59].

2.1.7. Other Genes

In the last decade, whole-exome and whole-genome sequencing studies identified somatic variants/alterations in various genes in PC samples [2,13,28,48,59], but the pathogenic role of all these genes in PC carcinogenesis is still unknown.

The genes identified in these studies are shown in Table 4.

Table 4. Genes whose somatic variants have been found in parathyroid carcinoma samples.

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
AADACL3	Not reported	Three missense mutations (p.Arg152His, p.Arg186Trp, p.Ala200Thr)	Arylacetamide Deacetylase-Like 3 (AADACL3)	Membrane protein predicted to enable hydrolase activity.	[47]
ACTB	Not reported	Three missense mutations (p.Cys17Tyr, p.Glu117Gln, p.Arg372His)	Actin Beta (ACTB)	This gene encodes one of six different actin proteins of the cytoskeleton, involved in cell motility, structure, integrity, and intercellular signaling	[47]
ADCK1	Proto-oncogene?	A recurrent heterozygote missense mutation (p.Ile482Met)	AarF Domain-Containing Kinase 1 (ADCK1)	Protein kinase?	[13]
AKAP9	TSG	Five missense mutations (p.Ser94Thr, p.Met159Ile, p.Glu341Val, p.Arg649Gln, p.Val1595Leu)) One nonsense mutation (p.Gln3379X)	A-Kinase Anchoring Protein 9 (AKAP9)	Binding protein to the regulatory subunit of protein kinase A, participating in multiple signal transduction pathways	[2,13,47]
ARID2	TSG	One inactivating truncating mutation (p.Gln1403X)	AT-Rich Interaction Domain 2 (ARID2)	DNA-binding protein, involved in transcriptional activation and repression of select genes by chromatin remodeling	[13]
ARID4A	Not reported	One frameshift indel (p.Lys512fs)	AT-Rich Interaction Domain 4A (ARID4A)	Bridging protein, recruiting histone deacetylases and regulating chromatin remodeling	[13]
ARID1B	Not reported	One missense mutation (p.Met910Lys)	AT-Rich Interaction Domain 1B (ARID1B)	Component of the SWI/SNF chromatin remodeling complex that may play a role in cell cycle activation	[2]
ATM	Not reported	One missense mutation (p.Ser1691Arg) One nonsense mutation (p.Leu1327X)	ATM Serine/Threonine Kinase (ATM)	Cell cycle checkpoint kinase	[2,59]
BRAF	Proto-oncogene	One missense mutation (p.Gly496Ala)	B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF)	Serine/threonine protein kinase, playing a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion	[2]
BRCA2	TSG	One missense mutation (p.Ser3133Leu)	BRCA2 DNA Repair Associated (BRCA2)	Protein involved in the maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA break repair.	[2]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
CCDC74A	Not reported	Two nonsense mutations (p.Gly230Ser *, p.Ser243Pro)	Coiled-Coil Domain-Containing 74A (CCDC47A)	Microtubule-associated protein	[47]
CENPF	Not reported	Two nonsense mutations (p.Ser1780X, p.Arg3094X)	Centromere Protein F (CENPF)	Component of the nuclear centromere–kinetochore complex, playing a role in chromosome segregation during mitosis	[2]
DCC	TSG	One missense mutation (p.Ser932Arg)	Netrin 1 Receptor (NTN1R1)	Transmembrane protein involved in cell adhesion	[59]
DDX11	Not reported	Three missense mutations (p.Arg186Trp, p.Gly345Arg, p.Pro798Val)	DEAD/H-Box Helicase 11 (DDX11)	Double-strand DNA helicase involved in DNA replication, DNA repair, heterochromatin organization, and ribosomal RNA synthesis	[47]
DFNB31 (WHRN)	Not reported	Two missense mutations (p.Met1Ile, p.Gly68Asp) One missense mutation (p.Ser12X)	Whirlin (WHRN)	Suspected to be involved in actin cystoskeletal assembly and stereocilia elongation and maintenance	[47]
EP300	Not reported	Two missense mutations (p.Gly1778Arg, p.Ile1786Val) One nonsense mutation (p.Arg1645X) One splicing site mutation (4779+1G>A)	E1A-Binding Protein P300	Histone acetyltransferase that regulates transcription via chromatin remodeling, important for regulating cell proliferation and differentiation	[48,59]
EPHB4	Not reported	One missense mutation (p.Glu733Gly)	EPH Receptor B4 (EPHB4)	Tyrosine kinase receptor for ephrins with an essential role in vascular development	[59]
ERBB4	Not reported	One nonsense mutation (p.Glu1260X)	Erb-B2 Receptor Tyrosine Kinase 4 (ERBB4)	Transmembrane tyrosine kinase receptor involved in regulation of cell mitogenesis and differentiation	[2]
ERC1	Not reported	Two missense mutations (p.Asn266Ser, p.Ser969Tyr)	ELKS/RAB6-Interacting/CAST Family Member 1 (ERC1)	Regulatory component of the Nf-kB signaling pathway	[2]
FAM20A	Not reported	One nonsense mutation (p.Tyr414X)	FAM20A Golgi Associated Secretory Pathway Pseudokinase (FAM20A)	Pseudokinase acting as an allosteric activator of the Golgi serine/threonine protein kinase FAM20C, involved in the regulation of biomineralization	[47]
FANCL	Not reported	One missense mutation (p.Leu254Val)	FA Complementation Group L (FANCL)	Ubiquitin ligase involved in DNA repair	[2]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
FAT3	TSG	Two homozygote inactivating nonsense mutations (p.Tyr293X, p.Leu126X) Four missense mutations (p.Pro996Ser, p.Glu2064Lys, p.Gly427Ser, p.Thr1483Met)	FAT Atypical Cadherin 3 (FAT3)	Predicted to be involved in cell–cell adhesion	[13]
FCGR2A	Not reported	One missense mutation (p.His167Arg) One splicing site mutation (not reported)	Fc Gamma Receptor IIa (FCGR2A)	Immunoglobulin Fc receptor expressed on the membrane of macrophages and neutrophils, involved in the process of phagocytosis of immucomplexes	[47]
FEV	Proto-oncogene	Two missense mutations (p.Met181Leu, p.Trp195Gly)	FEV Transcription Factor	Transcription factor exclusively expressed in in neurons of the central serotonin system	[47]
FLG2	Not reported	Three missese mutations (p.Ala818Ser, p.Ser2118Tyr, p.Ala2083Gly)	Filaggrin 2 (FLG2)	Protein involved in epithelial homeostasis, essential for normal cell–cell adhesion in the cornified cell layers	[47]
GLI3	Not reported	One nonsense mutation (p.Glu710X)	GLI Family Zinc Finger 3 (GLI3)	DNA-binding transcription factor, mediator of Sonic hedgehog (Shh) signaling·pathway	[2]
GRIN3A	Not reported	Two missense mutations (p.Glu771Gln, p.Asp1073Ile **)	Glutamate Ionotropic Receptor NMDA Type Subunit 3A (GRIN3A)	Subunit of the N-methyl-D-aspartate (NMDA) receptors, involved in physiological and pathological processes in the central nervous system	[47]
GUCY1A2	Not reported	One missense mutation (p.Ala257Thr)	Guanylate Cyclase 1 Soluble Subunit Alpha 2 (GUCY1A2)	Component of a soluble guanylate cyclase that that catalyze the conversion of GTP to 3′,5′-cyclic GMP and pyrophosphate	[59]
HLA-A	Not reported	Two missense mutations (p.Gly80Arg ***, p.Lys292Glu)	Major Histocompatibility Complex, Class I, A (HLA-A)	Member of the antigen-presenting major histocompatibility complex class IA for the for recognition by alpha-beta T cell receptor	[47]
HLA-B	Not reported	Two missense mutations (p.Arg180Trp *, p.Tyr140Ser)	Major Histocompatibility Complex, Class I, B (HLA-B)	Member of the antigen-presenting major histocompatibility complex class IB for the for recognition by alpha-beta T cell receptor	[47]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
HLA-C	Not reported	Three missense mutations (p.Asn104Lys, p.Ser101Asn, p.Arg121Trp)	Major Histocompatibility Complex, Class I, C (HLA-C)	Member of the antigen-presenting major histocompatibility complex class IC for the for recognition by alpha-beta T cell receptor	[47]
IL9R	Not reported	One missense mutation (p.Asn439Ser) One splicing site mutation (not reported)	Interleukin 9 Receptor (IL9R)	Receptor that specifically mediates the biological effects of interleukin 9, such as immune response against parasites	[47]
JMJD1C	TSG	One in-frame deletion (p.Lys593_Ser601del)	Jumonji Domain-Containing 1C (JMJD1C)	Histone demethylase, regulating chromatin remodeling	[13]
KDM4C	Not reported	One missense mutation (p.Arg919Lys)	Lysine Demethylase 4C (KDM4C)	Histone demethylase of lysine residues, regulating chromatin remodeling	[13]
KDM4E	Not reported	One missense mutation (p.Arg100His)	Lysine Demethylase 4E (KDM4E)	Histone demethylase of lysine residues, regulating chromatin remodeling	[13]
KDM5A	Not reported	One missense mutation (p.Ser1403Phe)	Lysine Demethylase 5A (KDM5A)	Histone demethylase of lysine residues, regulating chromatin remodeling	[48]
KDM5C	Not reported	Two missense mutations (p.Gly536Arg, p.Leu1549Val) Two nonsense mutations (p.Arg694X, p.Glu1475X9	Lysine Demethylase 5C (KDM5C)	Histone demethylase of lysine residues, regulating chromatin remodeling	[2,13,48]
KDM6A	Not reported	One missense mutation (p.Leu617Val)	Lysine Demethylase 6A (KDM6A)	Histone demethylase of lysine residues, regulating chromatin remodeling	[59]
KDR	Not reported	One missense mutation (p.Thr688Lys) One gene amplification	Kinase Insert Domain Receptor (KDR or VGRF2)	Tyrosine protein kinase that acts as a cell surface receptor for vascular endothelial growth factor (VEGFs), regulating angiogenesis	[48]
KIAA1549	Not reported	One missense mutation (p.Ala905Thr) One nonsense mutation (p.Trp1853X)	KIAA1549	Suspected to be involved in the regulation of oncogenic MAPK signaling	[2]
KMT2B	Not reported	One missense mutation (p.Arg1771Gln)	Lysine Methyltransferase 2B (KMT2B)	Histone methylase on lysine residues, regulating chromatin remodeling	[2]
KMT2C	Not reported	Two missense mutations (p.Leu3483Ser, p.Arg4523Ser)	Lysine Methyltransferase 2C (KMT2C)	Histone methylase on lysine residues, regulating chromatin remodeling	[2]
KMT2D	Not reported	Two missense mutations (p.Pro610Ala, p.Arg2830Gln)	Lysine Methyltransferase 2D (KMT2D)	Histone methylase on lysine residues, regulating chromatin remodeling	[2]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
LATS2	TSG	Two missense mutations (p.Ala428Thr, p.Lys793Met)	Large Tumor Suppressor Kinase 2	Serine/threonine protein kinase acting as regulator of YAP1 in the Hippo signaling pathway that plays a pivotal role in tumor suppression by restricting cell proliferation and promoting apoptosis	[2]
MAF	Proto-oncogene	Two missense mutations (p.Glu115Gln, p.His185Pro)	MAF BZIP Transcription Factor (MAF)	DNA-binding, leucine zipper-containing transcription factor, acting both as a transcriptional activator and repressor.	[47]
MAGI1	Not reported	One missense mutation (p. Glu1021Lys)	Membrane-Associated Guanylate Kinase, WW And PDZ Domain-Containing 1 (MAGI1)	Member of the membrane-associated guanylate kinase homologue that may play a role as scaffolding protein at cell-cell junctions	[59]
MAP1B	Not reported	Two missense mutations (p.Val1549Gly, p.Phe1838Leu)	Microtubule-Associated Protein 1B (MAP1B)	Microtubule-associated protein. Phosphorylated MAP1B may play a role in the cytoskeletal changes	[47]
MSH2	Not reported	One nonsense mutation (p.Gln545X)	MutS Homolog 2 (MSH2)	Component of the post-replicative DNA mismatch repair system	[2]
NCOR1	Not reported	Two missense mutations (p.Gln469Glu, p.Arg1129Gln)	Nuclear Receptor Corepressor 1 (NCOR1)	Mediator of transcriptional repression of thyroid hormone and retinoic acid receptors by promoting chromatin condensation	[47]
NEB		Six missense mutations (p.Val150Ile, p.Tyr773Cys, p.Ile2239Met, p.Val2751Ile, p.Lys3099Asn, p.Phe5555Leu, p.Asp5633Ile) One splicing site mutation (not reported)	Nebulin (NEB)	Giant protein component of the cytoskeletal matrix of cells of the skeletal muscle	[47]
NF1	TSG	Two nonsense mutations (p.Gly751X, p.Arg1748X) One frameshift mutation (p.Leu134fsX21)	Neurofibromin 1 (NF1)	Negative regulator of the ras signal transduction pathway	[2,48,59]
NOTCH1	TSG	One missense mutation (p.Thr194Pro) One inactivating nonsense mutation (Gln439X)	Notch Receptor 1 (NOTCH1)	Receptor involved in the Notch signaling pathway that regulates cell fate specification, differentiation, proliferation, and survival	[13]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
NRCAM	Not reported	Two missense mutations (p.Agr875Gln #, p.Asn1115Ser #)	Neuronal Cell Adhesion Molecule (NRCAM)	Ankyrin-binding protein involved in neuron–neuron adhesion and suspected also to play a general role in cell–cell communication via signaling from its intracellular domain to the actin cytoskeleton, during directional cell migration	[47]
NT5C1B-RDH14	Not reported	Two missense mutations (p.Arg146Gln, p.Glu221Gln)	NT5C1B-RDH14 Read-Through Transcript	Naturally occurring fusion protein, sharing sequence identity with the products of NT5C1B and RDH14 neighboring gene, presumably involved in the metabolism of nucleotides	[47]
NUP107	Not reported	Two missense mutations (p.Ser167Leu, p.Leu301met)	Nucleoporin 107 (NUP107)	Essential component of the nuclear pore complex that regulates in and out transport of all molecules to and from the nucleus	[2]
PDE4DIP	Not reported	Eight missense mutations (p.Pro30Ser, p.Pro50Leu, p.Pro155Arg *, p.Ala435Thr *, p.Asp759His, p.Gln1989Lys, p.Pro2355His, p.Lys2288Gln *)	Phosphodiesterase 4D Interacting Protein (PDE4DIP)	Protein acting as an anchor of phosphodiesterase 4D to the Golgi/centrosome region of the cell, participating in microtubule dynamics and assembly, responsible for polarized cell movement	[47]
PDPR	Not reported	One missense mutation (p.Thr29Ala *)	Pyruvate Dehydrogenase Phosphatase Regulatory Subunit (PDPR)	Regulatory subunit of the pyruvate dehydrogenase complex that catalyzes the oxidative decarboxylation of pyruvate during the glycolysis-related fatty acid synthesis	[47]
POLR2E	Not reported	One missense mutation (p.Ala102Val)	RNA Polymerase II, I And III Subunit E (POLR2E)	Subunit E of the RNA polymerase II, responsible for synthesizing messenger RNA	[2]
POLR2L	Not reported	One missense mutation (p.Ala34Thr)	RNA Polymerase II, I And III Subunit L (POLR2L)	Subunit L of the RNA polymerase II, responsible for synthesizing messenger RNA	[2]
POT1	Not reported	One missense mutation (p.Gln256Arg)	Protection Of Telomeres 1 (POT1)	Nuclear protein, member of a multi-protein complex that binds to the TTAGGG repeats of telomeres, regulating telomere length and protecting chromosome ends from recombination and chromosome instability	[59]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
PPP2R5D	Not reported	One missense mutation (p.Ile172Met [#]) One nonsense mutation (p.Gln51X [#])	Protein Phosphatase 2 Regulatory Subunit B'Delta (PPP2R5D)	Regulatory subunit B of a Serine/Threonine phosphatase 2A, implicated in the negative control of cell growth and division	[47]
PRKAR1A	Not reported	One missense mutation (p.Glu189Asp)	Protein Kinase CAMP-Dependent Type I Regulatory Subunit Alpha (PRKAR1A)	Regulatory subunit of the cAMP-dependent protein kinases involved in cAMP-mediated signaling in cells	[28]
PSMC3IP	Not reported	One nonsense mutation (p.Lys116X)	PSMC3 Interacting Protein (PSMC3IP)	Subunit of the PSMC3IP/MND1 complex, playing an important role in meiotic recombination	[2]
PTPRB	Not reported	One missense mutation (p.Arg1754Trp)	Protein Tyrosine Phosphatase Receptor Type B (PTPRB)	Protein tyrosine phosphatase, playing an important role in blood vessel remodeling and angiogenesis	[2]
RAD50	Not reported	Two missense mutations (p.Ile1227Met, p.Ser1244Cys)	RAD50 Double-Strand Break Repair Protein (RAD50)	Component of the MRN complex, involved in DNA double-strand break repair	[2]
RANBP9	Proto-oncogene?	Two missense mutations (p.Pro10Gln, p.Glu58Asp)	RAN-Binding Protein 9 (RANBP9)	Scaffold protein binding the RAN small GTP-binding protein, presumably acting as adapter protein to couple membrane receptors to intracellular signaling pathways	[47]
RFC5	Not reported	One missense mutation (p.Arg215Thr)	Replication Factor C Subunit 5 (RFC5)	Subunit 5 of the replication factor C complex, required for DNA replication	[2]
RNASEL	Not reported	One missense mutation (p.Ile1221Thr)	Ribonuclease L (RNASEL)	Component of the interferon-regulated 2–5A system with antiviral and antiproliferative function	[59]
SETD1B	TSG	One inactivating missense mutation (p.Ser1128Leu)	SET Domain Containing 1B, Histone Lysine Methyltransferase (SETD1B)	Histone methyltransferase, regulating chromatin remodeling	[13]
SUN2	Not reported	One missense mutation (p.Trp582Cys)	SUN Domain-Containing Protein 2 (SUN2)	Component of the LINC (LInker of Nucleoskeleton and Cytoskeleton) complex, involved in the connection between the nuclear lamina and the cytoskeleton	[2]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
SYCP2	Not reported	One missense mutation (p.Pro495Leu)	Synaptonemal Complex Protein 2 (SYCP2)	Major component of the axial/lateral elements of synaptonemal complexes that links homologous chromosomes during the prophase of meiosis	[2]
SYNE1	Not reported	Two missense mutations (p.Ile3456Met, p.Glu5956Gly)	Spectrin Repeat Containing Nuclear Envelope Protein 1 (SYNE1)	Spectrin repeat containing protein, which forms a linking network between organelles and the actin cytoskeleton to maintain the subcellular spatial organization	[2]
TJP2	Not reported	Two missense mutations (p.Arg24His, p.Glu1003His)	Tight Junction Protein 2 (TJP2)	Component of the tight junction barrier in epithelial and endothelial cells	[47]
TP53	TSG	Seven missense mutations (p.Lys132Asn, p.Arg181Cys, p.Arg248Trp, p.Arg273His, p.Arg283Cys, p.Gly334Trp, p.Arg337His) Four nonsense mutations (p.Glu51X, p.Arg342X, p.Gln375X, p.Arg306X) One splicing site mutation (783-1G>A)	Tumor Protein P53 (TP53)	Transcriptional regulator that, in response to cellular stress, regulates transcription of target genes inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism.	[2,48,59]
TRIO	Not reported	Two missense mutations (p.Pro67Ser, p.Asp2095His)	Trio Rho Guanine Nucleotide Exchange Factor (TRIO)	GDP to GTP exchange factor for GTPases, promoting the reorganization of the actin cytoskeleton and playing a role in cell migration and growth	[47]
TTK	Not reported	Two missense mutations (p.Ser108Thr, p.Glu361Lys)	Phosphotyrosine Picked Threonine Kinase (TTK)	Mitotic kinase able to phosphorylate proteins on serine, threonine, and tyrosine, essential for chromosome alignment at the centromere during mitosis and for centrosome duplication	[47]
TXNDC2	Not reported	(p.Ser147Gly, p.Ala225Pro, p.Ser237Gly *)	Thioredoxin Domain Containing 2 (TXNDC2)	Enzymatic domain with thioredoxin-disulfide reductase activity, involved in cell differentiation and cellular oxidant detoxification	[47]

Table 4. *Cont.*

Gene	Type of Tumor-Related Gene	Identified Mutation(s) in PC	Encoded Protein	Function of the Encoded Protein (Gene Cards)	Reference
VCAN	Not reported	Two missense mutations (p.Pro2996Thr, p.Gly3102Ser)	Versican	Large chondroitin sulfate proteoglycan, a major component of the extracellular matrix, involved in cell adhesion, proliferation, proliferation, migration, and angiogenesis	[2]
XAB2	Not reported	One missense mutation (p.Asp253Asn)	XPA-Binding Protein 2 (XAB2)	Component of the spliceosome, involved in the splicing process of mRNA	[47]
ZEB1	Proto-oncogene?	Three activating missense mutations (p.Gln467Glu, p.Gly956Ala, p.Glu244Lys)	Zinc Finger E-Box Binding Homeobox 1 (ZEB1)	Transcriptional repressor that mediates tumor invasion and metastasis by promoting ephitelial-mesenchymal transition	[13]
ZNF417	Not reported	(p.Arg322Gly * #, p.Tyr329Cys #, (p.Gln343X)	Zinc Finger Protein 417 (ZNF417)	Zinc finger protein predicted to be involved in regulation of transcription by RNA polymerase II.	[47]

TSG = Tumor suppressor gene. * = recurrent mutation in 2 unrelated patients out of 23 (8.7%) [47]; ** = recurrent mutation in 3 unrelated patients out of 23 (13.0%) [47]; *** = recurrent mutation in 4 unrelated patients out of 23 (17.4%) [47]; # = these two missense mutations were found in a single PC case [47].

Interestingly, the contemporary somatic complete deletion of the *CDKN2A* and *CDKN2B* genes, lying adjacent at the 9p21.3 locus, was described in two unrelated PC patients [48]. These two tumor suppressor genes encode two inhibitors of the cyclin-dependent kinases (CDKs), the Cyclin-dependent kinase inhibitor 2A (p16INK4A) and the Cyclin-dependent kinase inhibitor 2B (p15INK4B), which induce cell cycle arrest at G1 or G2 phases. The loss of these two cell cycle inhibitors could confer tumor cells an advantage in proliferation. The *CDKN2B* gene was published by Agarwal et al. as potentially implicated in hyperparathyroidism [77]. A possible role of the loss of tumor suppressor activity of *CDKN2A* and *CDKN2B* genes in parathyroid tumorigenesis was also suggested by the finding of promoter hypermethylation of these two genes in PC samples [78].

Two recurrent variants (−146C>T and −124C>T) in the promoter region of the *TERT* gene, encoding an enzyme with reverse transcriptase activity involved in the maintenance of telomer ends, were found at the somatic level, respectively, in two and three unrelated PC samples [48]. Interestingly, these two mutations were previously identified in 70% of melanoma [79], suggesting they could impair telomerase activity and have a shared role in oncogenesis in different tissues.

A recent gene expression study [80], profiling 740 genes known to be involved in main cancer-progression-related processes, was performed in metastatic and non-metastatic PCs, revealing two specific expression signatures of 87 (44 down-regulated and 43 up-regulated) and 103 (38 down-regulated and 65 up-regulated) genes, respectively characterizing non-metastatic PCs and metastatic PCs, compared to PAs. A specific sub-panel of significantly up-regulated (*ANGPTL4*, *BMP7*, *CD24*, *FGFR1*, *MMP9*, and *SOX2*) and down-regulated (*ERBB3*, *FBP1*, *RAB25*, and *TBX1*) genes was identified in metastatic PC, needing further investigation to better define the possible role of these deregulated genes in the malignant progression and metastatic potential of PC.

2.2. Epigenetics of Parathyroid Carcinoma

2.2.1. DNA Methylation

The hypermethylation of the CpG islands in the promoter regions of tumor suppressor genes, resulting in gene expression repression, was reported in various human malignancies, contributing to cancer development by activating cell proliferation.

Interestingly, in PC samples, hypermethylation was reported in promoters of various genes involved in the negative regulation of the Wnt pathway: (1) *SFRP1, SFRP2,* and *SFRP4* [78], encoding three antagonist decoy receptors of Wnt ligands; (2) *APC* [81], a tumor suppressor encoding a component of the beta-catenin destruction complex; (3) *RASSF1A* [81,82], a tumor suppressor whose silencing leads to the accumulation of active beta-catenin and activation of Wnt-signaling-regulated gene transcription; and (4) *HIC1* [83], encoding a transcription repressor that directly binds beta-catenin and the TCF4 transcription factor, preventing them from activating Wnt-induced TCF-mediated gene transcription. These findings seem to confirm the importance of constitutive/aberrant Wnt pathway activation in the pathogenesis of PC. All these gene promoters, except *HIC1*, were also hypermethylated in PA but not in normal parathyroid tissue. *APC, RASSF1A,* and *HIC1* were hypermethylated in 100% of analyzed PCs [81–83]. Conversely, the hypermethylation of the *CTNNB1* gene, encoding the beta-catenin, has only been reported in PAs to date [81].

The hypermethylation of promoters of the *GATA4* and the *PYCARD* genes was specifically found in PC [78]. The *GATA4* gene encodes a zinc finger transcription factor that regulates gene expression by binding to the GATA motifs in the promoters of many genes; the role of its silencing in PC tumorigenesis remains to be elucidated. The *PYCARD* gene encodes an adaptor protein that is involved in the regulation of apoptosis via the activation of caspases; the silencing of the *PYCARD* gene may confer parathyroid tumor cells the ability to escape apoptosis during carcinogenesis.

2.2.2. Chromatin Modification

Reversible modification of the chromatin structure regulates the accessibility of gene promoters to transcription factors, regulating gene expression, and it is due to post-transcriptional modifications of histones, such as methylation/demethylation, acetylation/deacetylation, and phosphorylation/dephosphorylation. Alterations in enzymes and regulatory molecules responsible for modifications of histones have been reported in cancers.

Parafibromin, which is commonly lost in both inherited and sporadic PCs, is a key regulator of histone modifications. Under normal conditions, parafibromin promotes, through direct interaction with the SUV39H1 histone methyltransferase complex, histone 3 methylation on lysine residues 4, 36, and 79 (H3K4me, H3K36me, and H3K79me, respectively), resulting in transcriptionally active chromatin, and on lysine residue 9 (H3K9me), which leads to transcriptional repression of the *CCND1* gene and cell cycle arrest. Moreover, by interacting with the RNF20/RNF40 ubiquitin ligase complex, parafibromin promotes the monoubiquitination of histone 2B on lysine residue 120, a modification that positively regulates RNA elongation during gene transcription.

Amplification of the *EZH2* gene at the 7q36.1 locus, encoding histone 3 lysine 27 methyltransferase, was found to be a common event in PC cases (about 60% of cases). A significant over-expression of EZH2 mRNA and protein was reported in malignant PC, with respect to both PAs and hyperplastic parathyroids [84], resulting in increased trimethylation of histone 3 on lysine residue 27 (H3K27me3) commonly associated with the repression of transcription of target genes. Among putative target genes of EZH2-mediated H3K27me3, there is *HIC1*, a tumor suppressor normally involved in the control of parathyroid cell proliferation, whose silencing through promoter hypermethylation was reported in one study in all five analyzed sporadic PCs [84]. Moreover, the EZH2 protein mediates the transcription repression of some Wnt signaling inhibitors, such as AXIN2, a component of the beta-catenin destruction complex, confirming once again that the activation of the Wnt signaling pathway appears to be an important pro-oncogenic event in parathyroid malignancies.

2.2.3. microRNAs

The deregulation of the expression of miRNAs, short non-coding RNA molecules that negatively regulate gene expression at the post-transcriptional level, has been reported in human malignancies, with both over-expressed miRNAs acting as oncogenes (oncomiR) or silenced/down-regulated miRNAs normally exerting tumor suppressor activity.

In agreement with the general behavior of miRNAs in cancer, PCs showed a globally lower expression of miRNAs than the normal parathyroid tissue [85].

miRNAs whose deregulated expression was specifically reported in PC compared to healthy parathyroid and benign PAs, their known target genes, and the possible role of the deregulated miRNA in PC tumorigenesis are summarized in Table 5.

Table 5. miRNAs whose expression was found to be deregulated in parathyroid carcinoma.

miRNA [Reference]	Known Target Gene(s)	Biological Activity of the Targeted Gene(s)	Effect of miRNA Altered Expression in Parathyroid Function, Parathyroid Tumorigenesis, and/or PC [Reference]
Down-regulated miRNAs in PC			
miR-26b [86]	*MYCBP*	Encoding the MYC-binding protein (MYCBP) that binds to the oncogenic protein c-MYC, enhancing the ability of c-MYC to activate E box-dependent transcription, increasing cell mobility	No studies available
miR-30b [86]	*TRIM27*	Encoding the tripartite motif-containing 27 protein (TRIM27) that activates the PI3K/Akt signaling pathway	No studies available
miR-126-5p [86]	*ADAM9*	Encoding the ADAM Metallopeptidase domain 9 (ADAM9) that cleaves and releases a number of molecules with important roles in tumorigenesis and angiogenesis. Suspected to mediate cell–cell, cell–matrix interactions and regulate the motility of cells via interactions with integrins	No studies available
	CRK (proto-oncogene)	Encoding the CRK adaptor protein that binds to several tyrosine-phosphorylated proteins and is involved in regulating cell adhesion, spreading, and migration	
	EGFL7	Encoding the epidermal growth factor-like protein 7 (EGFL7) involved in cell migration and angiogenesis	
	HOXA9	Encoding the Homeobox A9 (HOXA9) transcription factor involved in embryonic development, morphogenesis, and cell differentiation. Positive regulator of the eukaryotic translation initiation factor 4E (EIF4E) that promotes protein translation initiation	
	IRS1	Encoding the insulin receptor substrate 1 (IRS1), an intracellular signaling adaptor protein that integrates and coordinates numerous biologically key extracellular signals within the cell	
	KRAS (proto-oncogene)	Encoding the KRAS GTPase that activates the RAS/MAPK pathway inducing cell proliferation.	

Table 5. *Cont.*

miRNA [Reference]	Known Target Gene(s)	Biological Activity of the Targeted Gene(s)	Effect of miRNA Altered Expression in Parathyroid Function, Parathyroid Tumorigenesis, and/or PC [Reference]
miR-296-5p [85]	*PI3K*	Encoding the Phosphatidylinositol 3-Kinase (PI3K) that activates the PI3K-Akt pathway in response to a variety of growth factors, leading to cell proliferation	In human PC samples, miR-296-5p down-regulation resulted in increased HGS mRNA levels and in an immunostaining-detected dramatic over-expression of HSG [85].
	SLC7A5 (LAT1)	Encoding the SLC7A5 membrane protein of the intracellular organelles that acts as a neutral amino acid transporter	
	SOX2	Encoding the SRY-box transcription factor 2 (SOX2), involved in the regulation of embryonic development and in the determination of cell fate, required for pluripotent stem-cell maintenance	
	VEGF	Encoding the vascular endothelial growth factor (VEGF), a growth factor that induces proliferation and migration of vascular endothelial cells, essential for both physiological and pathological angiogenesis	
	HGS	Encoding the Hepatocyte growth factor-regulated Tyrosine kinase substrate that negatively regulates signal transduction mediated by cytokines and growth factors by inducing internalization and degradation of membrane receptors by lysosomes.	
Up-regulated miRNAs in PC			
miR-517C [87]	Not known	n.a.	Up-regulated miR-517C positively correlated in vivo with serum calcium and PTH levels, and with parathyroid tumor weight [87].
miR-371 [87]	PTEN (tumor suppressor)	Encoding the Phosphatidylinositol 3,4,5-Trisphosphate 3-Phosphatase protein (PTEN) that negatively regulates the AKT/PKB signaling pathway	No studies available
miR-372 [87]	*CDKN1A* (tumor suppressor)	Encoding the $p21^{cyp1}$ cyclin-dependent kinase inhibitor that inhibits the complex CDK2/CDK4, acting as a negative regulator of cell cycle progression at G1	miR-372 over-expression in parathyroid tumor cells increased PTH mRNA levels, and it positively correlated in vivo with circulating PTH levels. In parathyroid tumor cell miR-372 repressed the Wnt canonical pathway through the up-regulation of the Wnt antagonist DKK1 [88].
	LATS2 (tumor suppressor)	Encoding the large tumor suppressor kinase 2 (LATS2) that plays a critical role in centrosome duplication, maintenance of mitotic fidelity, and genomic stability, negatively regulates G1/S transition by down-regulating cyclin E/CDK2 kinase activity, and acts as negative regulator of YAP1 in the Hippo signaling pathway restricting cell proliferation and promoting apoptosis	

Table 5. *Cont.*

miRNA [Reference]	Known Target Gene(s)	Biological Activity of the Targeted Gene(s)	Effect of miRNA Altered Expression in Parathyroid Function, Parathyroid Tumorigenesis, and/or PC [Reference]
miR-222 [85]	*CDKN1B* (tumor suppressor)	Encoding the $p27^{kyp1}$ cyclin-dependent kinase inhibitor that inhibits the complex CDK2/CDK4, acting as a negative regulator of cell cycle progression at G1	In human PC samples, the up-regulation of miR-222 resulted in an almost complete loss of expression and nuclear localization of the $p27^{kyp1}$ protein [85].
miR-503 [85]	CCND1	Encoding the cyclin D1, a positive regulator of cell cycle that promotes the G1 to S phase transition through activation of CDK4 and CDK6	In human PC samples with up-regulation of miR-503, cyclin D1 displayed a heterogeneous immunoreactivity [85].

n.a. = not applicable; PTH = parathyroid hormone.

Out of these miRNAs, miR-296 was almost universally down-regulated in cancer compared to matched normal tissues, and it was often lost in metastatic lesions. The transcriptional profile of tumor cells with the down-regulation of miR-296 is enriched in multiple key regulators of cell motility, invasion, and metastasis [89], indicating this miRNA as a negative regulator of cell migration and suggesting its down-regulation as a marker of poor prognosis. miR-296 was also found to be down-regulated in lung metastasis from a PC [87].

Additionally, to these miRNAs specifically characterizing PC, miR-139-3p showed a similar expression in PC and PA, being significantly down-regulated in both parathyroid tumor types, with respect to the normal parathyroid tissue [85].

In addition to their intracellular localization, the presence of miRNAs has been reported in many biological fluids. miRNAs circulating in the blood (circulating miRNAs, c-miRNAs), both as free molecules and within exosomes, have recently attracted attention as possible high-quality biomarkers of human cancer [90]. Recently, Krupinova et al. [16] analyzed the expression of 754 c-miRNAs in the serum samples from 13 patients with PC and 11 patients with PA, finding 17 c-miRNAs to be significantly down-regulated in the PC group, including 1 miRNA whose down-regulated expression had been previously reported in PC samples [86], miR-126-5p. Among the 17 down-regulated c-miRNAs, miR-342-3p was the only one meeting the Benjamini–Hochberg criteria for multiple comparisons, and it appeared to be a potential diagnostic biomarker for the differential diagnosis of PC. Previous studies showed miR-342-3p as a miRNA with a potential tumor suppressor activity, crucial for the induction of apoptosis and inhibition of cell growth, tumorigenesis, and tumor cell invasion/migration. Currently, the role of the down-regulation of this miRNA in PC is still not known.

2.2.4. Long Non-Coding RNAs

LncRNAs are non-coding transcripts longer than 200 nucleotides, acting as epigenetic regulators of gene expression, mainly in a tissue-specific manner. Accumulating evidence indicates that the deregulated expression of lncRNAs may play a role in cancer biology [91].

Profiling analyses of lncRNAs in PC showed the down-regulation of lncRNA GLIS2-AS1 [92] and the up-regulation of lncRNA PVT1 [92] and lncRNA BC200 [93] in PC compared to PA, being able to distinguish between the two types of tumors.

The over-expression of lncRNA BC200 was reported in a broad spectrum of tumor cells, presumably being responsible for cell viability, invasion, and migration [94]. Interestingly, the over-expression of lncRNA BC200 not only distinguished between PCs and PAs, but this lncRNA was also significantly over-expressed in PC cases bearing *CDC73* mutations

compared to wild-type carcinomas, in association with a more aggressive clinical phenotype and characterized by higher levels of PTH and calcium [93], suggesting the existence of a pro-oncogenic circuit involving lncRNA deregulation and loss of the tumor suppressor *CDC73* that may have a role in parathyroid carcinogenesis and prognosis as an epigenetic modulator. Recently, Morotti et al. [95] quantified the expression of circulating lncRNA BC200 in the serum of 27 patients with PA and 4 patients with PC, showing significantly higher levels in the PC group. Moreover, a measurement of circulating lncRNA BC200 expression in the pre- and post-operative serum samples from 3 PC patients showed that the levels of this lncRNA in serum were significantly reduced after parathyroidectomy. These data suggested the over-expression of lncRNA BC200 as a hallmark of PC and the biochemical dosage of this molecule in the serum as a non-invasive suitable biomarker for initial PC diagnosis, tumor staging, and, possibly, clinical and therapeutic follow-up.

LncRNA PVT1 is encoded by the human *PVT1* oncogene, located at 8q24.21, and its transcription was shown to be regulated by the proto-oncogene *c-MYC* [96], which was demonstrated to promote lncRNA PVT1 accumulation in cancers. Increased copy number and over-expression of lncRNA PVT1 have been associated with various types of human malignancies [9]. Interestingly, lncRNA PVT1 was demonstrated to promote cancer cell proliferation in non-small cell lung cancer through the epigenetic regulation of large tumor suppressor kinase 2 (LATS2) by directly binding histone 3 lysine 27 methyltransferase EZH2, which was previously reported to be over-expressed by gene amplification in PC, acting as a pro-oncogenic factor in parathyroid carcinogenesis [84].

To date, the biological function of lncRNA GLIS2-AS1 is still unknown, and no reports in cancer or other human diseases are available.

2.3. Proteomics of PC

To date, only one proteomic study has been performed in PC, comparing the global protein expression profile between PC and PA coexisting in the same patient [97]. Validation was performed additionally in 10 PCs and 10 PAs. A subset of 33 differentially expressed proteins (10 down-regulated and 23 up-regulated) was found in the discovery PC sample and confirmed in the 10 additional PCs, including proteins mainly involved in cell signaling, cell metabolism, and ubiquitin-mediated protein degradation. In particular, PC was characterized, compared to PA, by the over-expression of Ubiquitin C-terminal hydrolase L1 (UCH-L1), a thiol protease involved both in the processing of ubiquitin precursors and ubiquitinated proteins, which recognizes and hydrolyzes proteins bound at the C-terminal glycine of ubiquitin. UCH-L1 was previously demonstrated to act as an oncoprotein in breast cancer, promoting/increasing tumor invasion and metastasis through the activation of the TGFβ [98], the MAPK/Erk [99], and the Akt [100] signaling pathways and enhancing multidrug resistance of cancer cells [99,101].

Other proteins that were specifically over-expressed in PC were 1) Chloride intercellular channel protein 1 (CLIC1), a nuclear chloride channel that is implicated in the activation of the cAMP-dependent protein kinase A that has been associated with cell growth and differentiation, cell–matrix adhesion, cell migration, and metastasis [102]; 2) Malate dehydrogenase 1 (MDH1), a cytosolic enzyme that catalyzes the NAD/NADH-dependent, reversible oxidation of malate to oxaloacetate in many metabolic pathways, and it has been shown to be over-expressed in cancer and associated with poor prognosis [103]; and 3) superoxide Dismutase (SOD2), a mitochondrial protein that destroys superoxide anion radicals derived from oxidative phosphorylation, which showed both tumor suppressive and promoting functions and whose over-expression was identified as a major protein change in fibroblasts associated with ovarian cancer cells [104].

Further studies on larger series of PCs and PAs, preferentially from the same patients to reduce the influence of exogenous confounding factors, are needed to confirm these results.

3. Therapy of Parathyroid Carcinoma

3.1. Current Therapies

3.1.1. Surgery

Surgery is the first-line therapy for PC. High pre-operative clinical suspicions of PC and/or the intra-operative identification of malignant features are fundamental in driving surgical management and are key to have a better curative chance. Pre-operative biopsy is contraindicated because of the high risk of tumor capsule rupture and tumor cell dissemination.

The surgical approach to PC consists of the en bloc resection of primary cancer with negative margins, usually associated with the excision of ipsilateral thyroid lobes and adjacent involved structures. Compartmental level VI lymph node dissection is indicated in case of metastatic tumor. The use of an intra-operative measurement of PTH is useful to confirm the removal of all hyperfunctioning parathyroid glands.

However, despite every surgical effort, disease recurrence occurs in over 50% of PC cases, and no specific therapeutic strategy is available to treat such patients.

Prophylactic parathyroidectomy to prevent PC in patients with germline *CDC73* mutations is not indicated, since not all carriers develop a malignant tumor. Bilateral exploration of the neck and the identification of all parathyroids glands, with resection of all affected gland(s), are the suggested approaches.

3.1.2. Adjuvant Therapies

Post-operative external beam radiation therapy is rarely used because PC is generally considered a "radioresistant" tumor. Data on the efficacy of radiation therapy on PC are contrasting and appear to be related to the tumor stage and the presence of local and distant invasion [105,106]. The treatment is prevalently restricted to palliative therapy of advanced metastatic disease.

Systemic cytotoxic chemotherapy is used even less frequently than radiotherapy and used only in a few extremely restricted cases, since it showed very limited benefits in inoperable PC patients and patients in whom surgery was ineffective, generally resulting in the inability to control tumor progression and functional tumor burden [106,107].

3.1.3. Therapies for the Control of Calcium Homeostasis

These pharmacological therapies are aimed to control PC-derived severe hypercalcemia before surgical intervention or in patients with inoperable and recurrent tumors or to mitigate the effect of post-operative permanent hypoparathyroidism after tumor resection.

The first-line treatment of hypercalcemia consists of intravenous hydration, diuretics, and anti-resorption drugs, such as bisphosphonates (typically intravenous administration of pamidronate or zoledronic acid) or denosumab, to inhibit osteoclast activity and reduce serum calcium levels.

In PC patients who do not respond to bisphosphonates or for whom the denosumab effect weakens over time, calcimimetic drugs, selective agonists acting on the calcium-sensing receptor on the membrane of parathyroid cells, can be used. Cinacalcet, a long-acting calcimimetic molecule, showed to be effective in reducing both serum calcium and PTH concentrations in about two-thirds of metastatic and inoperable PCs [108,109].

Post-operative chronic hypoparathyroidism and hypocalcemia require life-long therapy with calcium and active vitamin D.

3.2. Emerging Therapies

The administration of some medical therapies targeting molecular pathways showing alterations in a percentage of PC cases, which are currently approved for the treatment of different types of cancer but not PC, showed promising results in some case reports. These therapies need to be further evaluated and confirmed in larger PC case series.

3.2.1. Inhibitors of the PI3K/AKT/mTOR Pathway

Since somatic gene mutations that constitutively activate the PI3K/AKT/mTOR pathway were found in about up to 20% of PC cases [8], the use of PI3K/AKT/mTOR inhibitors could be effective in a subset of PC patients.

Kutahyalioglu et al. [59] treated a patient with a somatic mutation of the *TSC1* gene, a known regulator of the PI3K/AKT/mTOR pathway, and recurrent PC with liver metastasis by using a combination of everolimus (an mTOR inhibitor) and vandetanib (an antiangiogenic drug). Treatment allowed a stable disease, with better control of serum calcium levels, while on drugs.

Given the extreme rarity of PC, no randomized controlled clinical trial with PI3K/AKT/mTOR inhibitors has been conducted on this parathyroid cancer. "Basket trials", evaluating treatments in multiple cancer types sharing common alterations of the PI3K/AKT/mTOR genes, may help in overcoming the problem of patient rarity.

3.2.2. Inhibitors of Angiogenesis

The administration of drugs blocking angiogenesis showed promising results in some case reports in patients with PC.

Mutations in the *KDR* gene, encoding vascular endothelial growth factor receptor 2 (VEGFR2), were found in 13% of PCs [48]. After the identification of an activating somatic missense mutation (p.Thr688Lys) of the *KDR* gene in a patient with PC, Kang et al. [48] treated, sequentially, this patient with three inhibitors of VEGFR2, cabozantinib (a potent inhibitor of multiple receptor tyrosine kinases, including MET, RET, AXL, KIT, TIE2, and FLT3), ramucirumab (a monoclonal antibody against VEGFR2), and regorafenib (pleiotropic inhibitor of VEGFR1, VEGFR2, and TIE2). Cabozantinib treatment showed to reduce intact PTH (iPTH) and the size of the paratracheal lymph node over 3 months of treatment but induced various side effects, such as fatigue, hypertension, diarrhea, and epistaxis. After cabozantinib discontinuation, iPTH rose again. Treatment with ramucirumab failed to reduce iPTH levels. Treatment with regorafenib was well tolerated and effective in dropping the iPTH levels. Data from this case report indicate the benefit of performing genetic profiling of PC tumor samples to allow the choice of targeted therapy.

Based on the previously reported good response to the antiangiogenic sunitinib treatment in renal cell carcinoma patients with *KDM5C* mutations, Kutahyalioglu et al. [59] treated with sorafenib (an antiangiogenic multi-targeted tyrosine kinase inhibitor with a target profile similar to sunitinib) a patient with a somatic mutation of the *KDM5C* gene and persistent PC with lung metastases, which was not responsive to cinacalcet and intermittent doses of bisphosphonates. The treatment allowed good control of calcemia, even after the discontinuation of cinacalcet, for three years. Then, both PTH and calcium levels started to rise again with the progression of pulmonary metastases. The switch to a more potent antiangiogenic molecule, lenvatinib, granted a radiographically stable disease and good control of calcemia, without any calcimimetic administration, during the 20 months of therapy follow-up reported in the study.

Rozhinskaya et al. [32] positively treated, off-label, a *CDC73*-mutated woman with PC and multiple lung metastases by using sorafenib, an antiangiogenic multi-kinase inhibitor that blocks the activity of VEGFRs, resulting in the normalization of PTH and calcemia, the prevention of tumor progression, and a significant reduction in the size of lung metastases.

Very recently, Makino et al. [18] showed the effectiveness of combined therapy with sorafenib, denosumab, and evocalcet (a calcium-sensing receptor agonist) to treat refractory hypercalcemia in a *CDC73*-mutated patient with recurrent PC due to multiple lung metastases.

4. Conclusions

PC is an extremely rare malignant tumor of the parathyroid with aggressive behavior and a poor prognosis. The diagnosis of PC is still a challenge, and the exact pathogenesis is still largely unknown. In the last few years, advanced molecular techniques, such as

whole-exome sequencing, allowed researchers to identify specific genetic abnormalities and epigenetic features characterizing PC and distinguishing PC from benign PA. The identification and functional characterization of molecular drivers and deregulated pathways in PC carcinogenesis are crucial to the development of molecular therapy and novel targeted therapeutic agents to be used in advanced and metastatic inoperable tumors and/or in relapsing PC. Moreover, the identification of personal genetic alterations in the course of clinical care of PC patients could lead to tailored individualized treatments, consisting of rationally matched targeted agents, or immunotherapies, based on the genetic profile of each tumor.

The germinal and somatic loss/inactivation of the tumor suppressor parafibromin and the aberrant activation of the Wnt canonical pathway are two common hallmarks of PC, being suitable targets for tailored therapy in PC patients.

Inhibitors of the PI3K/AKT/mTOR pathway and antiangiogenic drugs showed promising positive results in selected PC case reports, both in the control of hypercalcemia and in the stabilization of cancer.

Unfortunately, the extreme rarity of PC cases and the variable spectrum of genetic and epigenetic alterations among affected patients prevented, to date, the performance of randomized controlled clinical trials to test targeted therapies. The institution of worldwide trials on relatively numerous PC patients is, thus, needed to prove the efficacy of genetics- and epigenetics-based treatments in reducing tumor growth and aggressiveness, and/or in controlling PC-associated refractory hypercalcemia.

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