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CYCLIN D1 IN PARATHYROID DISEASE

Sanjay M. Mallya and Andrew Arnold

Center for Molecular Medicine, University of Connecticut Health Center, Farmington, CT. USA

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1. ABSTRACT

Primary hyperparathyroidism (HPT), most commonly due to parathyroid adenoma, is a disorder characterized by excessive secretion of PTH. So far, abnormalities in two genes, *cyclin D1* and *MEN1*, have been implicated in the development of parathyroid adenomas. *Cyclin D1*, now an established *Oncogene* involved in numerous human cancers, was first identified and recognized as an *Oncogene* in the study of parathyroid tumors. A subset of parathyroid adenomas contains a clonal rearrangement that places the *PTH* gene's regulatory sequences in proximity to the *cyclin D1 Oncogene* causing its overexpression, and 20-40% of parathyroid adenomas overexpress the cyclin D1 protein. Transgenic animal models have further confirmed the role of *cyclin D1* as a driver of abnormal parathyroid cell proliferation. Future studies on the mechanism of *cyclin D1*'s oncogenicity and its interactions with other parathyroid growth regulators will further our understanding of parathyroid cell biology and may prove useful clinically.

2. INTRODUCTION

The parathyroid glands are endocrine organs that regulate calcium homeostasis. The major target organs of parathyroid hormone (PTH) are the bone and kidney. PTH increases bone resorption to mobilize calcium into the circulation. In the kidney, PTH enhances calcium reabsorption and decreases reabsorption of phosphate. PTH also stimulates renal production of 1,25-dihydroxyvitamin D3 [1,25 $(OH)_2$ D3], which in turn enhances intestinal absorption of calcium. Thus, the physiological effects of PTH increase the concentration of calcium in the circulation. Negative feedback from calcium and 1,25 $(OH)_2$ D3 modulate parathyroid function. Hypocalcemia causes increased PTH secretion and proliferation of parathyroid cells. These effects are mediated, at least in part, via the calcium-sensing receptor (CaR) expressed on the parathyroid cell surface. Similarly, 1,25 $(OH)_2$ D3, acting through its nuclear receptor, suppresses the synthesis of PTH and parathyroid cell proliferation. Thus, PTH secretion is tightly coupled to the parathyroid cell's ambient calcium level. States of abnormal parathyroid cell proliferation are typically associated with dysregulation of PTH secretion.

Primary HPT is a relatively common endocrine disorder with an incidence of approximately 1 per 1000 (1). It is characterized by hypersecretion of parathyroid hormone (PTH) and resultant hypercalcemia. Most cases of primary HPT (about 85%) result from a solitary adenoma in one of the parathyroid glands. Multi-gland hyperplasia is found in about 15% of primary HPT patients. Primary hyperplasia may occur sporadically or may be part of a familial HPT syndrome such as Multiple Endocrine Neoplasia (MEN) type 1 or 2A. HPT is also part of other inherited syndromes, such as the hereditary hyperparathyroidism jaw tumor syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHP) and familial hypocalciuric hypercalcemia (FHH). Very rarely, in less than 1% of patients, primary HPT is a consequence of parathyroid carcinoma.

Secondary HPT is an increase in PTH secretion as a physiological response to hypocalcemic states, for example in end stage renal disease or vitamin D-deficiency. Long-standing secondary HPT may lead to autonomous PTH secretion, a state where the parathyroid glands have ceased to respond appropriately to physiological regulation. This is referred to as refractory secondary HPT or tertiary HPT.

3. CLONING OF THE PRAD1/CYCLIN D1 ONCOGENE

The underlying molecular genetic pathology of parathyroid adenomas is only partially understood. The first clue to the nature of these lesions was provided by examinations of their clonality (2). These studies showed that parathyroid adenomas are monoclonal neoplasms, suggesting that these tumors are caused by mutations that alter the growth regulation of parathyroid cells. Other early molecular analyses revealed the presence of tumor-specific DNA rearrangements in a subset of adenomas--in such rearrangements the 5' *PTH* gene regulatory region becomes separated from its coding exons and was shown to recombine with a novel DNA locus, D11S287 (3). This rearrangement bore similarities to specific chromosomal translocations that occur in various B-cell lymphomas, wherein the tissue-specific regulatory sequences of the immunoglobulin heavy chain gene are juxtaposed with oncogenes like *BCL-2* or *C-MYC*, causing

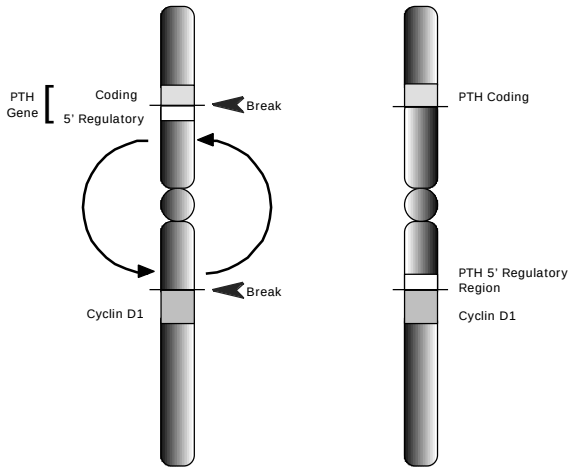

Figure 1. Schematic diagram of the pericentromeric inversion of chromosome 11. The rearrangement places the 5' PTH regulatory region upstream of the cyclin D1 gene.

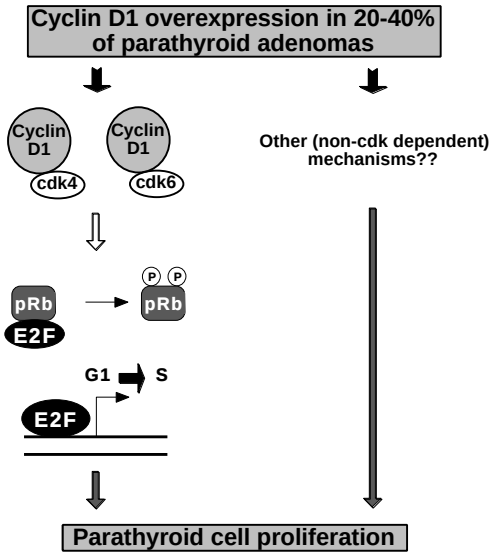

Figure 2. Schematic representation of oncogenicity of *cyclin D1* in parathyroid tumor cells. Based on the known function of cyclin D1 in cell-cycle regulation, cyclin D1 may possibly bind to cdk4 or cdk6, which phosphorylate pRb. Phosphorylated pRb dissociates from transcription factors in the E2F family, permitting transcription of genes involved in transition of the cell from G1 to S phase. Alternatively, other, non-cdk-dependent mechanisms may also be operational in these tumor cells.

their overexpression in the B-lineage cells. Thus, by analogy, it was expected that DNA from the non-*PTH* side of the breakpoint in the parathyroid tumors must harbor an *Oncogene* that provides the host parathyroid cell with a selective growth advantage. An mRNA transcript from this breakpoint-adjacent gene was identified and was found to be dramatically overexpressed in these parathyroid adenomas (4), suggesting that the tissue-specific enhancer elements of the *PTH* gene were indeed deregulating the expression of this putative oncogene. Subsequent cloning of this candidate *Oncogene* led to the identification of a novel gene (*PRAD1/Cyclin D1*) with sequence similarities to cyclins (5). The *PTH* gene is localized to chromosomal region 11p15, whereas the *cyclin D1 Oncogene* maps to 11q13 (3). Thus, the simplest explanation for this rearrangement is a pericentromeric inversion, inv(11)(p15;q13), that positions the 5' PTH regulatory region upstream of the *cyclin D1* gene (Figure 1). To date, *cyclin D1* is the only established parathyroid tumor oncogene.

Cyclin D1 was also cloned as a murine gene induced by growth factor exposure in a macrophage cell line (6) and as a cDNA capable of rescuing yeast made mutant in their G1-phase cyclins (7). The *cyclin D1* gene encodes a 35 kDa protein that shares structural homology and some functional properties with other cyclins (5, 7, 8). The cyclin D1 protein contains a retinoblastoma (pRB)-binding domain (9) as well as the conserved 'cyclin boxes'. Cyclin D1 complexes with and activates its kinase partners cdk4 and cdk6 in the G1 phase of the cell cycle. The activated kinases participate in the phosphorylation and inactivation of pRb, effecting entry into S-phase (Figure 2). Thus, inactivation of the tumor suppressive effects of pRb is one plausible mechanism for the oncogenic activity of cyclin D1. The *cyclin D1* gene is amplified in several human malignancies, including breast cancers (10-12) and head and neck carcinomas (13). Moreover, activating mutations of *CDK4* have been detected in human melanomas (14) and *CDK4* is amplified in sarcomas and gliomas (15, 16). Also, the cdk4-inhibitor p16 has been well established as a tumor suppressor. Thus, the cyclin D1 pathway is a central target in oncogenesis.

4. CYCLIN D1 IN PARATHYROID TUMORIGENESIS

As noted above, a subset of parathyroid adenomas contain clonal rearrangements that juxtapose the PTH 5' regulatory region with the *cyclin D1* gene. The 11q13 chromosomal breakpoint may be close to *cyclin D1* or may extend to as much as 300 kb centromeric of *cyclin D1* (Y. Hosokawa et al, unpublished data). This variability in the location of the breakpoint complicates standard approaches for detection of the rearrangement. Thus, there are no accurate estimates of the percentage of parathyroid adenomas that harbor such *cyclin D1*-activating rearrangements. However, as determined by immunohistochemistry, 20-40% of parathyroid adenomas overexpress cyclin D1 (17-19). In addition to the described chromosomal rearrangement, other molecular mechanisms for cyclin D1 overexpression such as gene amplification, rearrangement with other parathyroid-specific promoters or transcriptional activation may also be operational in these tumors.

In addition to the clonality of *cyclin D1* gene lesions, animal models have provided further evidence that cyclin D1 overexpression is indeed capable of driving parathyroid tumorigenesis. Our laboratory has generated a

transgenic mouse model for parathyroid neoplasia. These mice harbor a transgene in which the *cyclin D1* gene is placed under the control of the PTH regulatory region, thereby mimicking the rearrangement and resultant cyclin D1 overexpression observed in the human tumors. By the age of 6-10 months, these mice develop HPT, as evidenced by parathyroid enlargement and increased serum calcium and PTH levels (20). Thus, tissue-specific overexpression of cyclin D1 does induce parathyroid cell proliferation resulting in HPT.

Primary HPT is also a component of the inherited Multiple Endocrine Neoplasia syndromes, especially MEN-1. The *MEN1* gene was recently identified (21) and maps to chromosome 11q13, a region of frequent allelic loss in sporadic parathyroid tumors (22-26). Indeed, acquired inactivation of both alleles of the *MEN1* gene has been shown to contribute to 12-16% of parathyroid adenomas (27-29). The function of menin, the protein product of the *MEN1* gene, remains to be fully elucidated although evidence supports a role in transcriptional control (30). It was recently reported that sporadic adenomas with *MEN1* mutations have a marginally higher frequency of allelic losses and chromosomal imbalances compared with sporadic adenomas without involvement of the *MEN1* gene. Although these differences were not statistically significant, they suggest a possible role for *MEN1* in maintenance of chromosomal stability (31). Involvement of cyclin D1 in the pathogenesis of MEN 1-related tumors is unknown. It will be important to determine if there is cooperation between cyclin D1 and menin in the development of sporadic- and MEN1-related parathyroid neoplasia.

True malignancy involving the parathyroid is rare, especially so considering the common occurrence of benign parathyroid neoplasia. Differences in the regions of frequent chromosomal gains and losses between adenomas and carcinomas (26, 32, 33) suggest that the pathogenesis of these two lesions are different and that adenomas are not likely to be the precursors of the malignant neoplasm in this tissue. Immunohistochemical studies have detected overexpression of cyclin D1 in 50-91% of parathyroid carcinomas (17, 18), apparently even higher than that observed with parathyroid adenomas. The genetic basis for, and effect of, cyclin D1 activation in the context of parathyroid malignancy remains to be determined.

The molecular basis of severe secondary or tertiary HPT is poorly understood. Because of multigland involvement, it was assumed that this condition predominantly involves polyclonal (non-neoplastic) cellular proliferations. Although this is likely to be the case in the initial proliferative phase, it is now clear that monoclonal parathyroid expansion does occur in most patients with severe secondary or tertiary HPT (34, 35). However, immunohistochemical studies have not detected overexpression of cyclin D1 in parathyroid glands from patients with uremic HPT (19), suggesting an infrequent role for cyclin D1 in the development of this disease. Interestingly, acquired inactivation of the *MEN1* gene, also relatively common in sporadic primary HPT, seems to play only a minor role in the clonal expansion of these lesions (35, 36). Thus, the molecular genetic basis for the development of this clonal disease may differ from primary HPT.

5. FUTURE DIRECTIONS

To date, several other frequent genetic abnormalities have been reported in parathyroid adenomas, including loss of chromosomal regions on 1p, 1q, 6q, 9p, 11p, 11q, 13q and 15q and gain of chromosomes 16p and 19p (25, 26, 31, 32, 37, 38). However, genes located in these regions that contribute to neoplastic changes in the parathyroid gland remain to be identified.

Other than the still unproven possibility that pRb may be the tumor suppressor target of 13q deletions in parathyroid carcinomas (39), molecular analyses have failed to detect parathyroid tumor mutations in any of the other genes involved in the cyclin D1 pathway. Specifically, inactivating mutations or homozygous deletions of the p16 and p15 genes occur uncommonly, if ever, in parathyroid adenomas (38). These observations, plus other data suggesting that existing paradigms for cyclin D1 action in tumorigenesis may be too simplistic (40-42), raise the possibility that cyclin D1 may regulate parathyroid-cell growth via yet unknown mechanisms.

Finally, it should be emphasized that a hallmark of parathyroid adenomas is their loss of calcium sensitivity--an apparent resetting of the 'setpoint' mechanism that normally tightly couples PTH secretion with ambient calcium levels. However, mutations of the Ca++-sensing receptor gene have not been found in sporadic parathyroid adenomas (43). Further it is clear that primary deregulation of cyclin D1 can cause a secondary disturbance in the calcium-PTH secretory relationship (20, Imanishi et al, unpublished data). Examination of the contribution of cyclin D1 overexpression and other tumorigenic changes to deregulation of setpoint control will elucidate the critical links between proliferation and functional abnormalities in parathyroid neoplasia.

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Send correspondence to: Andrew Arnold, M.D., Center for Molecular Medicine, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030-3101, Tel:860-679-7640, Fax: 860-679-7639, E-mail: AArnold@nso2.uchc.edu

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