β-Catenin Expression in Thyroid Follicular Lesions: Potential Role in Nuclear Envelope Changes in Papillary Carcinomas

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Abstract

The morphologic distinction of benign and malignant thyroid follicular lesions can sometimes be challenging, therefore an immunohistochemical marker to aid in this distinction would be useful. β-Catenin is one such potential marker. It is part of a membrane-bound cell growth-signaling complex that plays a role in cell adhesion, as well as in promotion of growth through activation of the *Wnt* signaling pathway. Oncogenic signaling occurs when β-catenin is released, accumulates in the cytoplasm, translocates into the nucleus, and promotes transcription of genes including *bcl*-1 (cyclin D1) and *c-myc* that induce cell proliferation.

Paraffin blocks from 133 thyroidectomy specimens were stained with monoclonal antibodies reactive with β-catenin and cyclin D1. These included 53 cases of papillary thyroid carcinoma (PTC), 46 cases of follicular variant of papillary carcinoma (FVPC), 10 cases of follicular carcinoma (FC), and 24 cases of follicular adenoma (FA). Tissue from six normal thyroid specimens served as a control. The malignant lesions (PTC, FC, and FVPC) expressed strong cytoplasmic/nuclear staining and minimal residual membranous staining in 87%, 80%, and 71% of cases, respectively. In contrast, all normal thyroid tissue and 79% of FAs showed strong membranous reactivity with very minimal cytoplasmic staining. Interestingly, in 83% of PTC cases and 20% FVPCs, the intranuclear inclusions were distinctly β-catenin positive. Cyclin D1 over expression correlated with cytoplasmic relocalization of β-catenin in almost all cases, and no evidence of cyclin D1 gene amplification was observed.

β-Catenin can be of a diagnostic utility for thyroid lesions, because it highlights intranuclear inclusions in PTC, and shifts from a membranous localization to a cytoplasmic localization in malignant lesions. We speculate that the localization of β-catenin in intranuclear inclusions may reflect a cytoskeletal remodeling activity of β-catenin that is functionally significant for the PTC pathway.

Key Words: β-Catenin; cyclin D1; thyroid; papillary thyroid carcinoma; follicular carcinoma; follicular variant of papillary carcinoma; follicular adenoma; intranuclear inclusions.

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Introduction

The morphologic distinction between follicular adenoma (FA), minimally invasive encapsulated follicular carcinoma (FC), and follicular variant of papillary carcinoma (FVPC) can sometimes be challenging. FA is a solitary benign encapsulated mass containing follicles having uniform pattern, while FC shows vascular and/or capsular invasion with potential for distant metastasis [1,2]. FVPC is characterized by a follicular growth pattern with

the nuclear features of papillary thyroid carcinoma (PTC) [1,2]. PTC is characterized by a variety of ultrastructural features such as invagination of the nuclear envelope, which lead to the light microscopic appearance of intranuclear inclusions and nuclear grooves [1,2]. Therefore, an encapsulated follicular thyroid tumor with equivocal nuclear changes of PTC may be difficult to diagnose by morphology alone, and an immunohistochemical marker that may aid in this differential diagnosis would be useful.

β-Catenin plays a critical role in maintaining cell–cell adhesion, and it plays an incompletely characterized role in promotion of neoplastic growth. Cell–cell adhesion is established through its association with the cytoplasmic tail of E-cadherin in a complex that maintains cell polarity [3,4]. When β-catenin is dynamically released from its membrane association at cell junctions, it associates with glycogen synthase kinase-3 (GSK3), adenomatous polyposis coli (APC), and axin. β-Catenin is usually phosphorylated by GSK3 leading to its subsequent proteasomal degradation [5], or it can be sequestered by APC. Abnormalities of the degradation pathway, activation of the *Wnt* signaling pathway, mutations in APC, β-catenin genes, or tyrosine kinases can all lead to an increase in the level of free cytoplasmic β-catenin [6–8]. The free β-catenin is then translocated to the nucleus where it binds to the LEF-1/TCF complex that stimulates the transcription of target genes including *c-myc* and *bcl-1*, which could be relevant to carcinogenesis by virtue of their ability to promote entry into S phase [5,7]. β-Catenin also organizes actin and responds to, as well as regulates, tubulin dynamics [9], although the contribution of these cytoskeletal changes to the oncogenic activity of β-catenin is unclear.

Nuclear envelope irregularity in PTC is the result of irregular invaginations of the nuclear lamina and outer and inner nuclear membranes that appear to develop dynamically during interphase due to an imbalance of forces exerted on the nuclear envelope from chromatin or cytoskeletal elements [10,11]. The nuclear envelope irregularity together with the ground glass appearance of the nucleus, consisting of abundant euchromatin with smooth heterochromatin aggregates apposed to the nuclear lamina, are the key diagnostic traits of PTC [1,2]. A few studies have attempted to define the intranuclear inclusion bodies by immunohistochemistry, but no inclusion-specific antibody has been reported [12,13], although thyroglobulin was found in 10–30% of the cases in one study [14]. The aim of our study was to define the organization of β-catenin in papillary thyroid carcinoma, determine if β-catenin alterations were associated with transcriptional activation of the target gene cyclin D1, assess its potential role in nuclear envelope changes, and determine the diagnostic utility of the antibody for differentiating benign and malignant thyroid follicular lesions.

Materials and Methods

Specimen Selection

Paraffin blocks from 133 thyroidectomy specimens were selected from the surgical pathology files of the Department of Pathology at the University of Massachusetts Medical Center (U-MASS) and Department of Pathology at the Los Angeles County/University of Southern California Medical Center (LAC+USC). These included 53 cases of PTC, 46 cases of FVPC, 10 cases of FC, and 24 cases of FA. Six normal thyroid sections served as a control group. Some of these cases were

used in a previous study to correlate the expression of cyclin D1 and E2F-1 in benign and malignant thyroid lesions [15].

Immunohistochemistry

Routinely processed formalin-fixed paraffin-embedded tissue sections were used for immunohistochemical studies. Sections were mounted onto ChemMate capillary gap slides (Ventana Medical Systems Inc., Tucson, AZ), baked at 56°C for 60 min, deparaffinized with xylene, and rehydrated with ethanol to distilled water. Monoclonal antibodies reactive with β-catenin (C19220, 1:100, BD Transduction Lab., San Diego, CA) and cyclin D1 (P2D11F11, 1:20, Novocastra Laboratories Ltd./Vector Laboratories Inc., Burlingame, CA) were used. A heat-induced epitope retrieval method was employed prior to the immunostaining. Briefly, sections were placed in 0.01 *M* citrate buffer at pH 6.0 (Vector Laboratories, Inc.) and heated twice in a microwave oven for 5 min per cycle. The polyvalent secondary antibody used was detected with an avidin–biotin technique and 3',3'-diaminobenzidine-tetrahydrochloride dihydrate as the chromogen (Vector Laboratories, Inc.). A multitissue tumor block served as an external control for β-catenin, while sections of mantle cell lymphoma and normal tonsil were used as external positive and negative controls for cyclin D1. Two additional antibodies for β-catenin were used to validate our results, and the same staining methodology for both antibodies was utilized. The first was a monoclonal antibody (NCL-B-CAT, 1:100, Novocastra, New Castle, UK), while the second was a polyclonal antibody (RB-090-PI, 1:50, NeoMarkers, Fremont, CA).

Fluorescence *in situ* hybridization (FISH) was performed on 21 thyroid neoplasms including 15 papillary carcinomas and 6 follicular carcinomas in a previous study about the role of cyclin D1 and E2F-1 in benign and malignant thyroid lesions [15]. All cases in the previous study examined for FISH were used in our current study and were correlated with β-catenin expression.

Results

The pattern of β-catenin immunostaining in various thyroid lesions is summarized in Table 1. Nineteen out of 24 (79%) FAs showed strong membranous staining with minimal cytoplasmic staining (Fig. 1). Two cases showed strong cytoplasmic staining and three cases were negative. Eight out of 10 (80%) FCs showed strong cytoplasmic staining and minimal membranous staining (Fig. 2). One case was negative and the other had stronger membranous staining than cytoplasmic. Thirty-three out of 46 (71%) FVPCs expressed moderate to strong

Table 1. β-Catenin Immunostaining in Thyroid Lesions

	Membranous staining		Cytoplasmic staining		Nuclear staining		Inclusion bodies	
	Incidence	Intensity	Incidence	Intensity	Incidence	Intensity	Incidence	Intensity
Normal thyroid	100%	+++	0%	–	0%	–	0%	–
Follicular adenoma	79%	+++	8%	+	0%	–	0%	–
Follicular carcinoma	10%	+	80%	+++	Rare positive	+	0%	–
Follicular variant of papillary carcinoma	7%	+	71%	++	0%	–	20%	+
Papillary carcinoma	Minimal	+	87%	+++	Rare positive	+	83%	+++

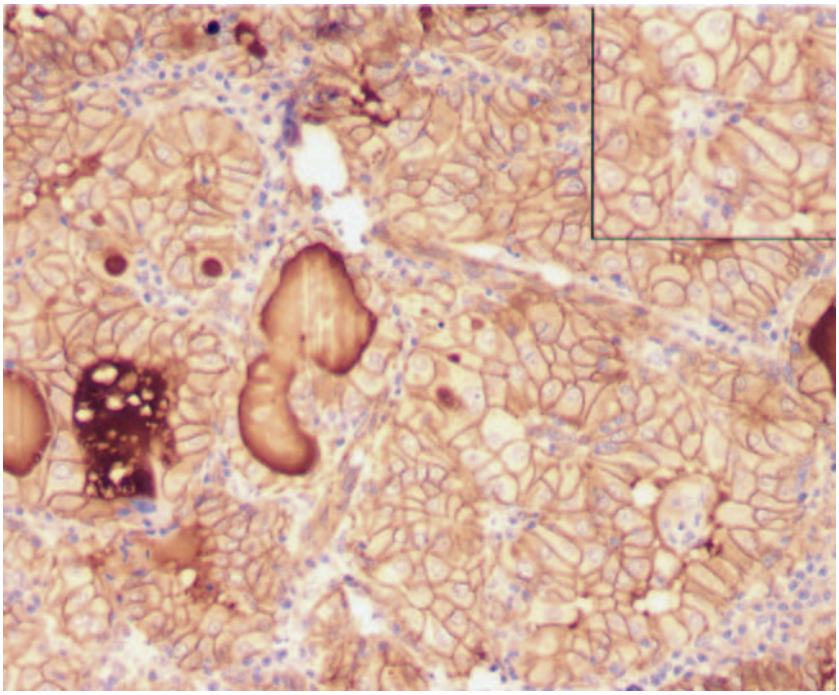

Fig. 1. Follicular adenoma showing strong membranous staining with β-catenin and no cytoplasmic reactivity. Inset demonstrating the membranous staining. (Immunoperoxidase at 10×.)

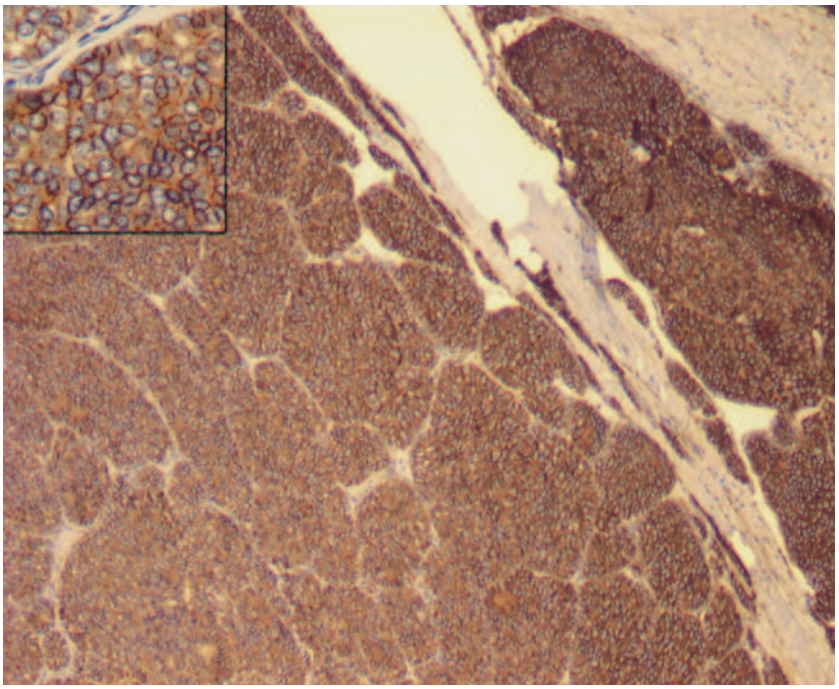

Fig. 2. Follicular carcinoma showing strong cytoplasmic staining with β-catenin and minimal membranous staining. Note that tumor cells are going beyond the capsule on the right corner of the picture. Inset showing cytoplasmic staining with minimal membranous staining. (Immunoperoxidase at 4×.)

cytoplasmic staining (Fig. 3), while the other 13 cases had minimal cytoplasmic expression, three of which had stronger membranous staining. It has to be noted that the cytoplasmic expression in FVPC was not as intense as in PTC and FC. Forty-six out of 53 PTCs (87%) showed strong cytoplasmic reactivity (Fig. 4). Rare nuclear staining was evident in some cases but not as intense as the cytoplasmic reactivity. The normal thyroid tissue control group showed membranous staining with complete absence of cytoplasmic or nuclear reactivity.

Interestingly, in 44 PTCs (83%) and 9 FVPCs (20%), the intranuclear inclusions were positive (Fig. 5). The intensity and number of positive inclusions varied from one case to the other without a relation to the staining intensity of the rest of the cell. In four cases, the inclusions were positive although there was hardly any cytoplasmic/nuclear staining (Fig. 6). There was no consistent correlation between the presence of β-catenin–labeled intranuclear cytoplasmic inclusions and cytoplasmic features, degree of nuclear envelope irregularity, tallness of the cells, chromatin morphology, or localization of the cells with respect to the leading invasive edge of the tumor. Furthermore, no apparent difference in tumor size or rate of lymph node metastases distinguished those PTC cases with and without β-catenin staining of inclusions.

Because cyclin D1 is one of the target genes for β-catenin, we used a monoclonal antibody for cyclin D1 in 15 PTCs, 4 FCs, and 7 FAs to correlate it with the expression of β-catenin. Thirteen out of 15 PTCs (87%) had nuclear positivity equivalent to the cytoplasmic/nuclear staining for β-catenin. The other two cases showed more reactivity with β-catenin than with cyclin D1, which was almost negative.

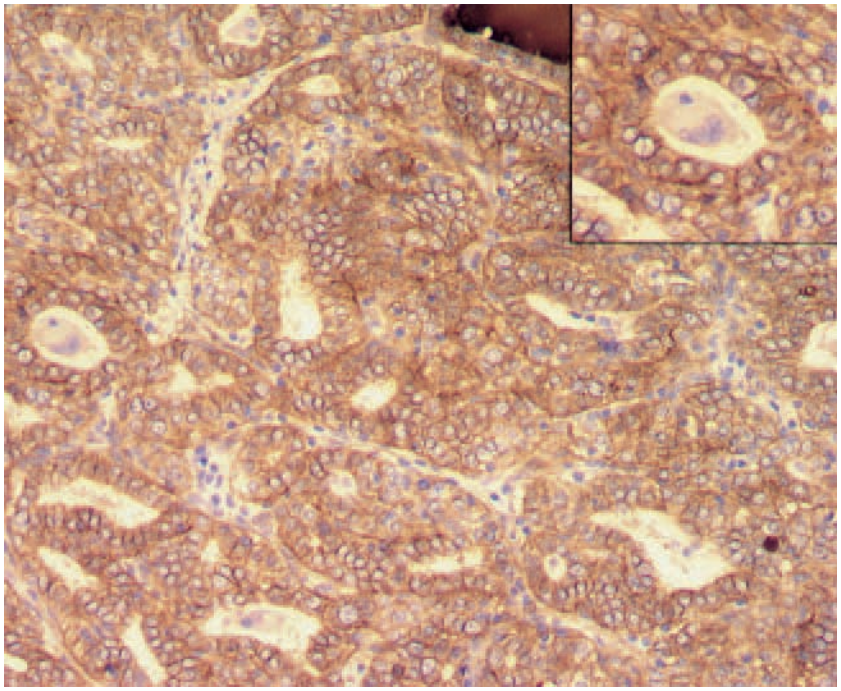

Fig. 3. Follicular variant of papillary carcinoma showing moderate cytoplasmic staining with β-catenin and some residual membranous staining. Inset showing cytoplasmic staining with minimal membranous staining. (Immunoperoxidase at 10×.)

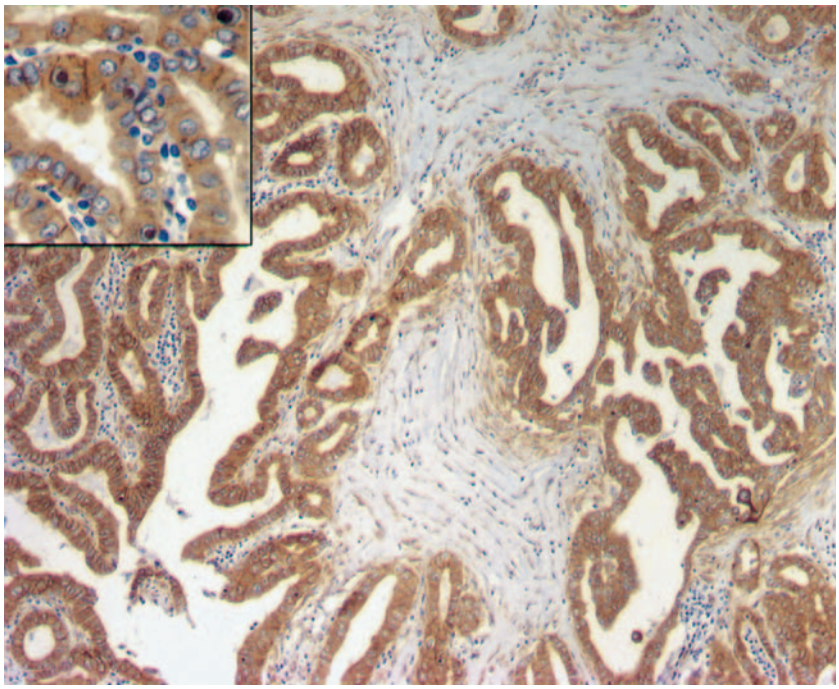

Fig. 4. Papillary carcinoma showing moderate to strong cytoplasmic staining with β-catenin and some residual membranous reactivity. Note the scattered positive intranuclear inclusions that are evident even at low power. Inset showing cytoplasmic staining with minimal membranous staining and scattered positive inclusion bodies. (Immunoperoxidase at 10×.)

All four cases of FC showed nearly identical results with both antibodies. Five out of seven FAs (71%) showed negative or weak nuclear staining with cyclin D1 that correlated with the membranous staining of β-catenin, while the other two cases had mild to moderate nuclear expression. We examined FISH results from a previous study [15] in 15 papillary and 6 follicular carcinomas with cyclin D1 overexpression, which were also utilized for our current study to determine if the cyclin D1 upregulation could be accounted for by a cytoplasmic redistribution of β-catenin, or whether cyclin D1 gene amplification was required for its upregulation. Each case in which β-catenin was relocalized to the cytoplasm showed more than 95% of the cells with two centromeric signals for chromosome 11, and no case showed evidence of 11q13 amplification

In summary, membranous staining was more evident in normal thyroid and in follicular adenoma cases, and decreased in intensity in PTC and follicular carcinoma. The cytoplasmic/nuclear β-catenin immunostaining was strongly expressed in carcinoma while it showed mild expression in follicular adenoma. The intranuclear inclusions were positive in the majority of PTC cases and in some FVPC cases.

Discussion

β-Catenin plays a role in cell–cell adhesion, serving as the intracellular domain of the E-cadherin complex that provides a link between cadherins and the actin cytoskeleton [16]. Another role of β-catenin is in the *Wnt* signaling pathway; the accumulation of free β-catenin in the cytoplasm leads to its translocation to the nucleus where it associates with lymphocyte enhancing factor (LEF-1) producing a β-catenin / LEF-1 complex that activates transcription

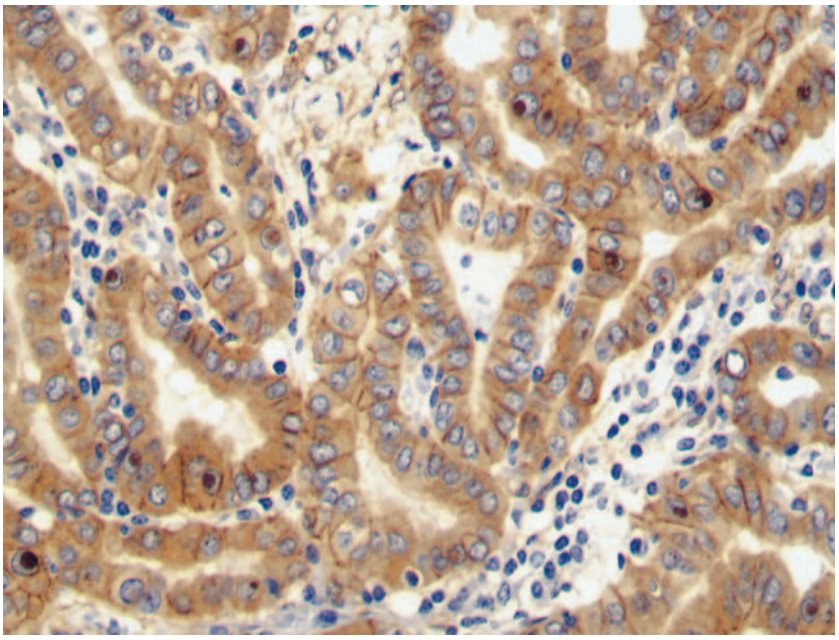

Fig. 5. High magnification picture of papillary thyroid carcinoma exhibiting cytoplasmic reactivity to β-catenin and clearly positive intranuclear inclusions. Note that the cells that contain positive inclusions have no apparent nuclear reactivity. (Immunoperoxidase at 60×.)

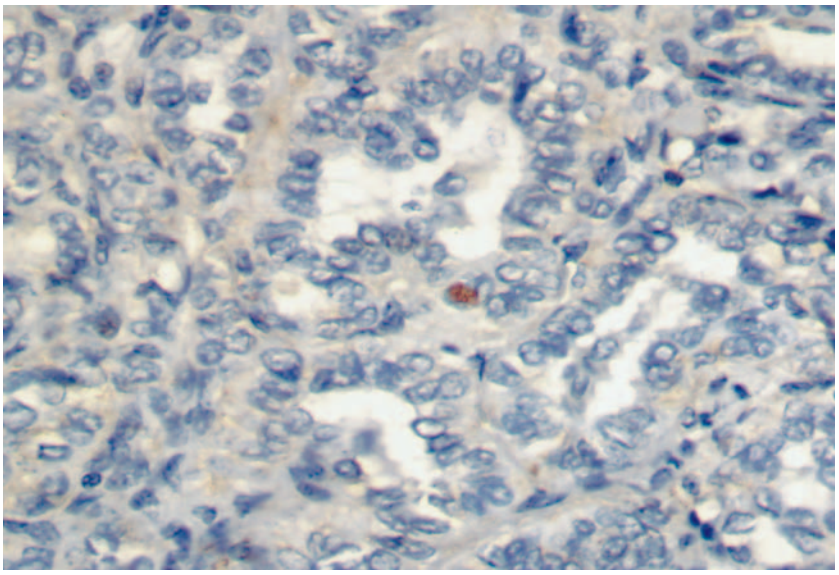

Fig. 6. Papillary thyroid carcinoma with negative cytoplasmic and membranous reactivity to β-catenin that contain a clearly positive inclusion in the center of the picture. (Immunoperoxidase at 60×.).

of target genes as *bcl*-1 and *c-myc* in the nucleus [17].

Aberrant *Wnt* signaling pathway leading to abnormal expression of β-catenin has been reported in many tumors including colon cancer [18], gastric cancer [19], hepatocellular carcinoma [20], prostate cancer [21], melanoma [22], and breast cancer [23]. In the absence of a translocation or amplification of the *bcl*-1 gene (cyclin D1), altered expression of β-catenin is the main activator of cyclin D1 in both colon cancer [24] and breast cancer [23]. Altered expression of β-catenin leading to overexpression of cyclin D1 in malignant thyroid lesions, especially PTC has been reported [18,25].

In our study, we followed the sequential progression of β-catenin expression from a membranous localization in benign lesions to cytoplasmic/nuclear localization in malignant follicular thyroid lesions. Membranous staining of β-catenin was strongly evident in follicular adenoma and residual normal thyroid. This membranous staining appears to have diminished in the malignant lesions. The reduction of membranous reactivity is consistent with the progressive disruption of intracellular adhesions that could be related to the invasive and metastatic properties of thyroid cancer cells [26]. Loss of β-catenin membranous immunoreactivity and its cytoplasmic/nuclear localization in thyroid has been found to correlate with loss of differentiation and poor prognosis in some studies [26,27].

The benign lesions (adenomas) showed weak cytoplasmic and no nuclear staining while the papillary and follicular carcinomas expressed strong cytoplasmic positivity for β-catenin. Nuclear positivity was observed in few cases but was not as intense as the cytoplasmic reactivity in PTC and FC. Nuclear positivity has been reported to be more evident in the poorly differentiated and undifferentiated thyroid carcinomas, and is usually associated with marked reduction or complete loss of membranous staining [26]. Frequent

β-catenin mutations and strong nuclear localization have been observed in many cases of anaplastic thyroid carcinoma [25,27]. The pattern of β-catenin staining in the different thyroid lesions in our series is consistent with *Wnt* signaling via translocation of β-catenin from the cell membrane to the nucleus, preferentially in malignant lesions.

Several studies have explored the effect of accumulated β-catenin on cyclin D1 gene activation in thyroid carcinogenesis [18,28,29]. We correlated the cytoplasmic/nuclear expression of β-catenin to the nuclear expression of cyclin D1 to confirm whether the well-described classical activation of cyclin D1 was present or that β-catenin can have functional significance entirely independent of its classical activation of cyclin D1. We also performed FISH to exclude the 11q13 amplification of cyclin D1. No evidence of amplification at the 11q13 locus was identified, and both antibodies had similar patterns of expression in adenomas and carcinomas.

An interesting observation in our study, which has not been previously reported, was the evident β-catenin positivity of the intranuclear inclusions in PTC and some cases of FVPC. Intranuclear inclusions were first described by Soderstorm et al. in 1973 as well-defined, clear, round intranuclear inclusions bounded by condensed chromatin and occupying at least 10% of the nuclear surface area [30]. Ultrastructurally, they result from partial invaginations of the cytoplasm into the nucleus [1,31]. They are bounded by an unremarkable outer and inner nuclear membrane and have an intact underlying nuclear lamina [10]. Although very characteristic for PTC, the intranuclear inclusions can be occasionally identified in other thyroid lesions including medullary thyroid carcinoma [32], Hashimoto's thyroiditis [31,33], and multinodular goiter [34]. Gamachi et al. among others reported the presence of intranuclear inclusions in pregnancy-related endometrium and studied the reactivity of the intranuclear inclusions to β-catenin; however, they failed to identify any β-catenin positivity in spite of the presence of evident nuclear staining [35].

The majority of our PTC cases (88%) showed strong staining of the intranuclear inclusion bodies, while only 20% of the FVPC cases had positive inclusions. The number of positive inclusions varied from one case to another without any relation to the intensity of the staining of the rest of the cell. The positivity of the inclusions cannot be explained by overstaining, because the intensity and number of positive inclusions did not correlate with the intensity of the cytoplasmic/nuclear staining of β-catenin. Four cases had positive inclusions despite the fact that they had almost negative cytoplasmic/nuclear staining. Furthermore, our results were validated by using two additional antibodies for β-catenin (monoclonal and polyclonal). Also, we obtained the same positive reactivity of the intranuclear inclusions at both U-MASS and USC laboratories.

The precise co-localization of the β-catenin with intranuclear inclusions suggests that β-catenin may be related to the development of these inclusions. Because β-catenin is involved in organizing actin and microtubule polymerization [36], it is possible that these cytoskeletal elements emanating from a β-catenin focus could push on the nuclear envelope and lead to the formation of an inclusion.

In conclusion, β-catenin can be of a diagnostic utility in the diagnosis of thyroid lesions because it highlights intranuclear inclusions in papillary thyroid carcinoma, and shifts from a membranous localization to a cytoplasmic localization in follicular as well as papillary thyroid car-

cinomas. We speculate that the localization of β-catenin in intranuclear inclusions may reflect a cytoskeletal remodeling activity of β-catenin that is functionally significant for the papillary thyroid carcinoma pathway.

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