Association of Nuclear, Cytoplasmic Expression of Galectin-3 With β-Catenin/Wnt-Pathway Activation in Thyroid Carcinoma

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Objectives: To characterize the localization of galectin-3 in benign and malignant thyroid neoplasms and to correlate this with alterations in β-catenin and cyclin D1 expression.

Design: Immunohistochemical study of 116 paraffin-embedded archival specimens from 113 patients who had undergone thyroidectomy and tissue placed into a commercially available tissue microarray.

Setting: Tertiary care hospital.

Interventions: Thyroid tissue microarrays were stained by standard immunohistochemical protocols with monoclonal antibodies against galectin-3, β-catenin, and cyclin D1.

Main Outcome Measures: Nuclear and cytoplasmic expression of galectin-3 was correlated with clinical parameters, β-catenin, and cyclin D1 expression.

Results: Both cytoplasmic (56%) and nuclear (42%) galectin-3 expression was observed in most malignant neoplasms but was absent in benign thyroid specimens (P<.001). Among carcinomas, cytoplasmic galectin-3 expression was observed in papillary thyroid carcinomas (82%) and follicular (33%) and medullary (9%) carcinomas but was absent in anaplastic carcinomas (P<.001). Galectin-3 nuclear expression was observed in papillary thyroid carcinomas (62%) and follicular carcinomas (33%) but was undetectable in medullary, anaplastic carcinomas (P<.001). Cytoplasmic but not nuclear galectin-3 was inversely correlated with American Joint Committee on Cancer TNM stage (P=.02). There was a strong correlation between cytoplasmic and nuclear β-catenin expression and both nuclear (P=.04) and cytoplasmic (P=.003) galectin-3 expression. Similarly, there was a strong association between galectin-3 nuclear (P<.001) and cytoplasmic (P<.001) expression and cyclin D1 expression.

Conclusion: Cytoplasmic and nuclear galectin-3 expression seem to be associated with activation of the Wnt-signaling pathway in well-differentiated thyroid neoplasms, suggesting that galectin-3 plays a role in thyroid carcinogenesis.

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APPROXIMATELY 18,000 NEW cases of thyroid carcinoma are diagnosed annually in the United States, of which papillary thyroid carcinoma (PTC) accounts for the vast majority (70%-80%). Other types of thyroid carcinomas include follicular, medullary, and anaplastic (undifferentiated) carcinoma. Most thyroid carcinomas are characterized by thyroid nodules, but most thyroid nodules (95%) are benign. Even with use of fine-needle aspiration, distinguishing benign from malignant thyroid nodules remains problematic. Although most cases of PTC are relatively easy to identify historically, some can present significant challenges. In addition, the distinction of follicular carcinoma or follicular-variant of PTC from benign follicular adenoma is not possible based on fine-needle aspiration alone. Therefore, the continued search for molecular markers of differentiated thyroid cancer is of great significance.

One possible molecular marker for thyroid malignancy is galectin-3. The galectins are a group of galactoside-binding lectins expressed in a variety of normal human cell types. They have been implicated in tumor progression for a variety of malignancies, including thyroid, colon, prostate, endometrial, gastric, and lung cancers. Data are accumulating that indicate galectins play important roles apart from their cytoplasmic and extracellular carbohydrate-binding function. Nuclear
expression of one member of the galectin family, galectin-3, has been shown to result in transcriptional up-regulation of thyroid transcription factor TTF-1. Moreover, transfection of galectin-3 into normal thyroid follicular cells has been shown to induce malignant transformation. Based on immunohistochemical studies, cytoplasmic galectin-3 is known to be overexpressed in PTC to a varying extent, and it has been proposed as a possible diagnostic marker for PTC.

Recently, it has been suggested that galectin-3 may be an important mediator of the β-catenin/Wnt pathway. With regard to its role in oncogenesis, β-catenin function has been explored extensively in the context of colorectal adenocarcinoma. β-Catenin exists in distinct subcellular locations and fulfills 2 distinct roles: it is membrane bound (where it mediates cytoskeleton/adhesion functions by interacting with E-cadherin) and it is a cytoplasmic constituent. Cytoplasmic β-catenin is usually short lived because it is rapidly degraded by a proteasome-mediated process. It can, however, be stabilized in response to Wnt-signaling, whereupon it may translocate to the nucleus. There, it binds to T-cell factor proteins to stimulate Wnt target genes. Cyclin D1 (an integral regulator of early cell-cycle progression) has been proposed as one of the multitude of target genes affected by Wnt pathway activation.

Evidence is accumulating that nuclear galectin-3 may play a role that is distinct from that of cytoplasmic galectin-3. In tongue cancer, nuclear galectin-3 expression was shown to be decreased compared with normal tongue epithelium, whereas cytoplasmic galectin-3 expression was increased. In contrast, growing fibroblasts demonstrate both nuclear and cytoplasmic galectin-3, whereas senescent fibroblasts display cytoplasmic but lack nuclear galectin-3. Therefore, the role of nuclear galectin-3 in carcinogenesis remains unclear. Although the presence of nuclear galectin-3 in thyroid cancer has been reported anecdotally, to our knowledge, no investigations specifically have addressed the incidence of nuclear galectin-3 in a large-scale series of thyroid neoplasms.

We undertook the present study to examine the cytoplasmic and nuclear expression of galectin-3 using a tissue microarray--based study of 116 benign and malignant thyroid specimens. We sought to correlate galectin-3 expression with alterations in β-catenin membranous (non-Wnt signaling) and cytoplasmic/nuclear (Wnt signaling) expression and cyclin D1 expression.

**IMMUNOHISTOCHEMICAL ANALYSIS**

Slides were deparaffinized and stained using standard immunohistochemical protocols. In brief, slides were deparaffinized in xylene followed by absolute ethanol and subsequent rehydration in graded 95% and 70% ethanol. Following a brief rinse in deionized water, heat-induced antigen retrieval was performed using sodium citrate buffer at pH 6.0 at 95°C for 20 minutes. Endogenous peroxidase was blocked with 0.3% hydrogen peroxide in methanol for 5 minutes at room temperature. The following primary antibodies were used: galectin-3 (monoclonal mouse clone abm-c10; Research Diagnostics Inc, Flanders, NJ), β-catenin (monoclonal mouse clone 14; BD Biosciences, Rockville, Md), and cyclin D1 (monoclonal mouse clone DSC-6; Dako, Carpinteria, Calif). Slides were incubated at room temperature with primary antibody as specified: galectin-3 (1:100 dilution, 30 minutes), β-catenin (1:500 dilution, 30 minutes), and cyclin D1 (1:100 dilution, 30 minutes). Subsequently, slides were incubated with a goat anti-mouse secondary antibody conjugated to a horseradish peroxidase--decorated dextran polymer backbone (Envision GM, Dako) for 30 minutes at room temperature. The antibody was subsequently visualized using 3,3’-diaminobenzidine (DAB chromagen; Dako) for 10 minutes at room temperature followed by acidified hematoxylin counterstain. Slides were mounted with Cytoseal 60 (Richard-Allan Scientific, Kalamazoo, Mich). Negative (no primary antibody) controls as well as positive controls were included for each antibody studied. Positive controls were as follows: for galectin-3, normal breast tissue with additional internal controls consisting of nerve fascicles and tissue macrophages; for β-catenin, colon cancer; and for cyclin D1, colon cancer.

Protein expression status was independently and blindly determined by 3 investigators (P.M.W., R.J.B., and J.R.L.). Subsequently, consensus scoring using a multihead microscope was used to resolve any discrepancies. Galectin-3 was evaluated separately for cytoplasmic and nuclear expression on a 4-point scale: 0 for no or minimal or focal (<10%) staining, 1+ for light staining (>10% of cells), 2+ for moderate staining (>10% of cells), or 3+ for heavy staining (>50% of cells). β-Catenin expression was evaluated for both membranous and nonmembranous (cytoplasmic and/or nuclear) expression as a dichotomous score: weak (no or very light staining) vs strong (moderate to intense staining). Cyclin D1 expression was evaluated based on percentage of nuclei of any intensity expressing cyclin D1: 0 (<5%), 1+ (5%-25%), 2+ (25%-50%), or 3+ (>50%).

**STATISTICAL ANALYSIS**

For ease of comparison, galectin-3 and cyclin D1 expression were dichotomized into underexpressors (0-1) vs overexpressors (2-3). Complete TNM staging was not available for all cancers; therefore a dichotomized TNM staging comparing early stage (stage I or stage II) with advanced stage (stage III or stage IV) was used based on the 2002 AJCC staging system. Comparison of galectin-3 expression by tumor type was made by contingency table analysis with Fisher exact test. Comparison of galectin-3, cyclin D1, and β-catenin expression by age was made using the standard t test. Comparison of galectin-3, cyclin D1, and β-catenin expression by malignancy, sex, and dichotomized TNM stage was made by contingency table analysis with Fisher exact test. Correlation of galectin-3 cytoplasmic and nuclear expression with β-catenin and cyclin D1 expression was also made using contingency table analysis with Fisher exact test. All calculations and analyses were 2-tailed where appropriate and were performed with SAS statistical software (JMP 6.0 for Windows; SAS Institute, Cary, NC).

**METHODS**

**PATIENT SELECTION**

Commercially available tissue microarrays (model A210 thyroid array; Abxis Co Ltd, Seoul, South Korea; and model TH802 thyroid array; Biomax USA Inc, Rockville, Md) were used for analysis. Deidentified data sets with age, sex, pathologic diagnosis, TNM stage (when known and according to the 2002 American Joint Committee on Cancer [AJCC] staging system) and histopathologic description were also obtained from the companies. This protocol was reviewed and approved by the Medical College of Georgia, Augusta, institutional review board.

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RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL PARAMETERS

Tissue from 116 patients comprised the study group (17 [15%] were men; 96 [83%], women; and 3 patients [2%] for whom sex was not recorded). The patients ages ranged from 18 to 79 years (median, 42 years). Histologically, 61 patients (52%) had thyroid carcinomas: 35 (30%) PTCs, 13 (11%) follicular, 11 (9%) medullary, and 2 (2%) anaplastic. Forty-eight patients (41%) had benign thyroid adenomas, and 7 (6%) had normal thyroids. We were able to determine TNM staging (early stage vs advanced stage) for 34 (56%) of the 61 carcinomas. There were 28 early-stage carcinomas (82%) and 6 advanced-stage carcinomas (18%). Demographic and clinical parameters are summarized in the Table.

GALECTIN-3 EXPRESSION

Galectin-3 expression was evaluated in 59 (97%) of 61 malignant and 55 (100%) of 55 benign thyroid specimens. Galectin-3 expression could be classified in both a cytoplasmic (Figure 1A) and a nuclear distribution (Figure 1B). Cytoplasmic galectin-3 was overexpressed in 33 (56%) of 59 malignant neoplasms vs 0 of 55 benign thyroid specimens (P<.001). Among carcinomas, elevated cytoplasmic galectin-3 expression was observed in 28 (82%) of 34 PTCs, 4 (33%) of 12 follicular, 0 of 11 medullary, and 0 of 2 anaplastic carcinomas (P<.001). There was an inverse relationship between TNM stage and cytoplasmic galectin-3 expression but not nuclear galectin-3 expression. One (17%) of 6 advanced-stage tumors had elevated galectin-3 cytoplasmic expression, compared with 20 (74%) of 27 early-stage tumors (P = .02). There was no relationship between age, sex, and galectin-3 cytoplasmic or nuclear expression. These results are summarized in the Table.

GALECTIN-3 SENSITIVITY AND SPECIFICITY

The sensitivity and specificity of galectin-3 nuclear and cytoplasmic staining for classifying PTCs was evaluated. Among all specimens evaluated, galectin-3 cytoplasmic staining had a sensitivity of 56% and a specificity of 100%. Galectin-3 nuclear staining had a sensitivity of 42% and a specificity of 100%. The sensitivity and specificity of galectin-3 nuclear and cytoplasmic staining for PTC were also evaluated by comparing galectin-3 staining among benign disease and PTCs only (excluding the follicular, medullary, and anaplastic carcinomas). For distinguishing PTC from benign disease, galectin-3 cytoplasmic staining had a sensitivity of 82% and a specificity of 100%, whereas galectin-3 nuclear staining had a sensitivity of 62% and a specificity of 100%.

β-CATENIN EXPRESSION

β-Catenin expression was evaluated in 61 malignant and 55 benign thyroid specimens. β-Catenin expression was noted in both membranous (non-Wnt signaling)

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**Table. Demographic, Clinical, and Pathologic Data**

<table>
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<tr>
<th>Characteristic</th>
<th>Patients, No.</th>
<th>Galectin-3 Cytoplasmic*</th>
<th>Galectin-3 Nuclear*</th>
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<td>Low/High Expression, No.</td>
<td>P Value</td>
<td>Low/High Expression, No.</td>
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<td>.73</td>
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<td>Male</td>
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<td>12/5</td>
<td>&gt;.99</td>
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<tr>
<td>Female</td>
<td>96</td>
<td>0/28</td>
<td></td>
</tr>
<tr>
<td>Not recorded</td>
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<td></td>
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</tr>
<tr>
<td>Pathologic finding</td>
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<td>Papillary carcinoma</td>
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<td></td>
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<td>Medullary carcinoma</td>
<td>11</td>
<td>0/1</td>
<td>&lt;.001‡</td>
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<tr>
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</table>

*Galectin-3 staining could not be determined in 2 patients.†Age range, 18 to 79 years (median age, 42 years).‡Significant at the P<.01 level.¶For malignancies only. Staging was performed according to the criteria of the American Joint Committee on Cancer.§Significant at the P<.05 level.‖Significant at the P<.001 level.
cytoplasmic or nuclear localization (indicating accumulation of Wnt-pathway signaling β-catenin) (Figure 2B). Strong membranous β-catenin expression was observed in 28 (46%) of 61 malignant neoplasms and 17 (31%) of 55 benign thyroid specimens \((P = .13)\). Among carcinomas, strong β-catenin membranous expression was observed in 13 (37%) of 35 PTCs, and 7 (54%) of 13 follicular, 6 (55%) of 11 medullary, and 2 anaplastic carcinomas \((P = .25)\). Cytoplasmic, nuclear β-catenin expression was highly associated with malignant disease and was observed in 46 (75%) of 61 malignant neoplasms vs 24 (44%) of 55 benign thyroid specimens \((P < .001)\). Among carcinomas, β-catenin cytoplasmic and nuclear expression was observed in 29 (83%) of 35 PTCs, and 9 (69%) of 13 follicular, 6 (55%) of 11 medullary, and 2 anaplastic carcinomas \((P = .21)\). There was no correlation between β-catenin cytoplasmic, nuclear, or membranous localization and TNM stage, age, or sex.

CYCLIN D1 EXPRESSION

Cyclin D1 expression was evaluated in 61 (100%) of 61 malignant and 55 (100%) of 55 benign thyroid specimens. Cyclin D1 expression was noted to be nuclear in localization (Figure 3). Cyclin D1 expression was strongly correlated with malignant disease and was observed in 25 (41%) of 61 malignant neoplasms vs 4 (7%) of 55 benign thyroid specimens \((P < .001)\). Among carcinomas, cyclin D1 expression was observed in 16 (46%) of 35 PTCs, 6 (46%) of 13 follicular, 2 (18%) of 11 medullary, and 1 (50%) of 2 anaplastic carcinomas \((P = .41)\). There was no correlation between cyclin D1 expression and TNM stage, age, or sex.

CORRELATION OF GALECTIN-3 WITH β-CATENIN AND CYCLIN D1 EXPRESSION

For the entire cohort there was no correlation between membranous β-catenin and galectin-3 cytoplasmic \((P = .40)\) or nuclear \((P = .35)\) localization (Figure 4). By contrast, there was a strong correlation between cytoplasmic or nuclear β-catenin and cytoplasmic galectin-3 localization. Twenty-seven (82%) of 33 specimens (malignant and benign) with elevated galectin-3 cytoplasmic expression had cytoplasmic or nuclear β-catenin expression vs 42 (52%) of 81 specimens that lacked galectin-3 overexpression \((P = .003)\). Similarly, 20 (80%) of 25 specimens with nuclear galectin-3 expression exhibited cytoplasmic/nuclear β-catenin expression vs 49 (55%) of 89 specimens that lacked nuclear galectin-3 expression \((P = .04)\) (Figure 4).

Cyclin D1 expression was strongly correlated with both cytoplasmic and nuclear galectin-3 expression. Eighteen (59%) of 33 specimens (malignant and benign) with el-
Elevated galectin-3 cytoplasmic expression exhibited cyclin D1 expression vs 9 (11%) of 81 specimens that lacked galectin-3 overexpression \( (P<.001) \) (Figure 4). Similarly, 14 (56%) of 25 specimens with nuclear galectin-3 expression showed cyclin D1 expression vs 13 (15%) of 89 specimens that lacked nuclear galectin-3 expression \( (P<.001) \) (Figure 4). There was a strong correlation between both membranous \( \beta \)-catenin \( (P=.004) \) and cytoplasmic or nuclear \( \beta \)-catenin \( (P<.001) \) and cyclin D1 expression.

Our data suggest that there is a strong association between both cytoplasmic and nuclear galectin-3 expression and markers for activation of the Wnt-signaling pathway. This is evidenced by the strong correlation of both nuclear and cytoplasmic galectin-3 expression with aberrant expression of \( \beta \)-catenin as well as downstream tar-

**Figure 2.** \( \beta \)-Catenin expression. \( \beta \)-Catenin, specifically cytoplasmic and nuclear expression, was highly correlated with malignancy. A, Papillary thyroid carcinoma (PTC) demonstrating strong membranous \( \beta \)-catenin expression. B, The PTC displays cytoplasmic and nuclear expression of \( \beta \)-catenin. This is indicative of Wnt-pathway activation. C, The PTC with decreased \( \beta \)-catenin expression. D, Follicular adenoma displaying decreased \( \beta \)-catenin expression. For all panels, the target expression was visualized with 3,3’-diaminobenzidine (DAB chromagen; DAKO, Carpinteria, Calif) and hematoxylin counterstain (original magnification ×20).

**Figure 3.** Cyclin D1 expression. Cyclin D1 (nuclear expression pattern) was highly correlated with malignancy. A, Papillary thyroid carcinoma (PTC) demonstrating strong cyclin D1 expression. B, The PTC lacks cyclin D1 expression. C, Normal thyroid demonstrating lack of cyclin D1 expression. The target expression was visualized with 3,3’-diaminobenzidine (DAB chromagen; DAKO, Carpinteria, Calif) and hematoxylin counterstain (original magnification ×20).
get cyclin D1. It is important that we found no correlation between membranous (non-Wnt signaling) β-catenin and galectin-3. Our findings are in agreement with Shimura et al., who proposed that galectin-3 may be an important mediator of the β-catenin/Wnt pathway. In addition to finding structural homologies between GSK3-β-catenin binding domains in β-catenin and galectin-3, they demonstrated that stimulation of cyclin D1 by β-catenin may be galectin-3 dependent. The results of our study lend support to this hypothesis.

In our cohort, the association between galectin-3 and cyclin D1 was stronger than that between galectin-3 and cytoplasmic/nuclear β-catenin. This may indicate that galectin-3 mediates cyclin D1 up-regulation through...
β-catenin–dependent pathways as well as β-catenin–independent pathways. Recently, Sansom et al14 studied the effects of adenomatous polyposis coli (APC) loss on cyclin D1 levels in murine intestinal adenoma formation. Loss of APC is known to be an early event in the progression of colorectal adenomas to carcinomas. Cyttoplasmic β-catenin is stabilized by loss of APC, and thus activation of the Wnt-signaling pathway occurs following loss of APC. Sansom et al14 found that following induced APC loss, cyclin D1 levels did not immediately change, although dysregulation of β-catenin could be clearly demonstrated. Cyclin D1 levels did rise secondarily, and it was proposed that the CCND1 (the gene for cyclin D1) promoter may indeed have T-cell factor binding sites but also requires other factors to enhance transcription. Transcriptional activation of the CCND1 promoter region by galectin-3 has been suggested by one study.15 It is interesting to note that individuals with familial adenomatous polyposis (FAP) syndrome are at dramatically increased risk of developing PTC in addition to the intestinal manifestations of the disease.16 The presence of FAP with extracolonic manifestations is referred to as Gardner syndrome. In FAP and/or Gardner syndrome, patients carry an autosomal dominant mutation in the APC gene. Women with FAP have a 160-fold increased risk of developing thyroid cancer with greater than 90% of those cancers having PTC histologic traits.17 To our knowledge, no studies of galectin-3 expression in patients with FAP or Gardner syndrome have been performed to date.

It has been suggested that galectin-3 immunostaining represents an acceptable clinical test for differentiating malignant thyroid neoplasms from adenomas and may spare the patient thyroid surgery.6,18 Although the avoidance of surgical resection for benign disease is an admirable goal, it is imperative to realize that a preoperative sensitivity for diagnostic tests of even 90% is unacceptable if such testing is to be the sole determinant of the need for surgery. The incidence of thyroid cancer in the United States is approximately 18 000 new cases per year.2 If the decision to avoid thyroidectomy were based on a preoperative test with 90% sensitivity, this would represent 1800 patients annually with true thyroid carcinoma who did not undergo treatment with surgical resection. It could be expected that this would increase the risk of a poor outcome for these patients, who otherwise have a largely favorable prognosis. Our findings of 56% sensitivity and 100% specificity for cytoplasmic expression of galectin-3 are in concordance with previous studies of galectin-3 immunohistochemical findings in thyroid neoplasms. We therefore agree with other authors6,21–24 that galectin-3 immunostaining is not an acceptable screening test for preoperative clinical decision making in the treatment of thyroid nodules. With 1 exception,19 most studies demonstrate reduced or absent galectin-3 expression in benign thyroid specimens.6,21–24 We propose that galectin-3 immunostaining may be a useful adjunct in interpreting difficult pathologic cases, especially for confirming suspected malignant neoplasms, given its excellent specificity.

We found a significant inverse correlation between cytoplasmic but lack nuclear galectin-3 expression, whereas senescent fibroblasts display cytoplasmic but lack nuclear galectin-3 expression.12 Concordant results have been seen in human breast epithe-
lial cell lines.\textsuperscript{33} It is possible that nuclear galectin-3 has multiple effects that are both tumor promoting and tumor inhibiting. Further studies investigating the role of nuclear galectin-3 in thyroid carcinoma are needed.

This study has several limitations, primarily related to the retrospective nature of the investigation. Our findings are based on tissue microarray-based immunohistochemical analysis of archival paraffin-embedded specimens. As a result, our data are observational and do not prove causality. A relationship between galectin-3 expression and the Wnt-signaling pathway is thus suggested by this data but unproven. The small number of healthy controls and subjects with non-PTC limits statistical analysis of galectin-3 expression in these specimens. Finally, the lack of clinical data with respect to tumor size and follow-up limits the conclusions that can be drawn from this work. However, this pilot study suggests that galectin-3 may play a significant role in thyroid carcinogenesis. Additional studies to investigate the role of galectin-3 as well as other galectins, β-catenin, and cyclin D1 in thyroid carcinoma seem warranted and are currently under way in our laboratory.

In conclusion, galectin-3 expression seems to have a strong correlation with β-catenin and cyclin D1 in thyroid carcinoma. These data suggest that galectin-3 may be involved in the development of well-differentiated thyroid carcinoma through activation of the Wnt-signaling pathway. Additional studies to test this hypothesis are warranted.

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REFERENCES


