Expression of MUC4, MUC 15, MMP-13, and TIMP-3 in papillary thyroid carcinoma

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Expression of MUC4, MUC15, MMP-13, and TIMP-3 in papillary thyroid carcinoma

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Papillary thyroid carcinoma (PTC) is the most frequent malignancy among thyroid carcinomas. The aim of this study is to investigate the expression of membrane mucins *MUC 4 and MUC15*, and *MMP-13* and *TIMP3* which has regulatory effects on MMP-13 activity in PTC, and to examine their clinicopathological correlations, such as invasive and metastatic characteristics.

We analyzed the expression of *MUC4, MUC15, MMP-13,* and *TIMP-3* between 10 PTC and 10 normal thyroid tissues using real time reverse transcription-polymerase chain reaction. A tissue array block was made using tissue from 98 cases of PTC tissue and immunohistochemical study was conducted using sectioned slides from the tissue array block. The semiquantitative scoring was compared with the clinicopathological factors to evaluate the prognostic significance in PTC patients.

MUC4- and *MUC15*- specific mRNAs increased approximately by 78-fold and 4.75-

fold respectively in PTC compared to normal thyroid tissues. *MMP-13* and *TIMP-3* gene expression decreased approximately by approximately 0.39-fold and 0.53-fold respectively. *MUC4* and *MUC15* protein expression increased in PTC compared to normal thyroid tissues (P<0.001). *MMP-13* and *TIMP-3* protein expression decreased in PTC compared to normal thyroid tissues (P<0.001). The *MUC4* high scores significantly correlated with small tumor size, and papillary thyroid microcarcinoma subtype. The *MUC15* high scores significantly correlated with age (≥45 years), distant metastasis, and multifocality.

The present study of PTC suggests that membrane mucins *MUC4* and *MUC15* were overexpressed in PTC, and high levels of *MUC15* expression was associated with high malignant potential. *MUC15* may serve as a prognostic marker and may be a potential novel therapeutic target in this disease.

Key words: MUC4, MUC15, matrix metalloproteinase 13, TIMP3, papillary thyroid carcinoma, expression

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Ⅰ. INTRODUCTION

Papillary thyroid carcinoma (PTC) arising from normal follicular cells is the most frequent carcinoma of the thyroid gland and is generally associated with slow growth and good prognosis. However, some cases show a relatively early recurrence, severe invasion, multiple lymph node metastasis or distant metastasis. It would be important to identify the characteristics of thyroid carcinoma which have a high risk for invasion and metastasis.

Mucins comprise a heterogenous family of highly glycosylated, high-molecular-weight glycoproteins that are characterized by extensively O-glycosylated tandem repeats that are rich in serine and threonine residues. To date, at least 20 mucin genes have been reported and are designated chronogically in the order of discovery.[1-3] Complete or partial sequencing of mucin genes has led to the classification of mucins into gel-forming mucins (MUC2, MUC5AC, MUC5B, MUC6, MUC19), soluble mucins (MUC7,MUC9) and membrane-associated mucins (MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC13,

MUC14, MUC15, MUC16, MUC17, MUC20), with MUC8 and MUC11 remaining unclassified.[4] These unique glycoproteins are typical of epithelial cells and are believed to exert a primary protective function of epithelial and mesothelial tissue linings. This protective function may, however, also be exploited by tumor cells for their defense against immunological attack.[5-7] Several studies proposed MUC1 as a key molecule in the pathogenesis of thyroid carcinoma (TC).[8-12] In addition, MUC1 overexpression facilitated faster turnover of Met. Phosphorylation of MUC1 cytoplasmic tail by Met enhanced its interaction with p53, which led to suppression of AP1 transcription factor activity through interactions at MMP1 promoter, ultimately leading to reduced transcription of MMP1.[13] On the basis of this result, we chose matrix metalloproteinases (MMPs) and their inhibitor, TIMP as candidate genes besides mucins in our study.

MMPs are enzymes that play a role in tumor development by promoting various events including degradation of extracelluar matrix.[14] There are various types of MMPs such as collagenases, gelatinases, stromelysins, matrilysin, and membrane-bound MMPs based on the specificity of substrates.[14] A previous study demonstrated that expression and activities of MMP-2 and MMP-9, and their inhibitors TIMP-1 and TIMP-2 increased in tumor cells of PTC.[15] Other study suggested that MMP-7, and MMP-11 are inversely linked to aggressive characteristics of PTC.[16]

The aim of this study is to investigate the expression of membrane mucins MUC 4 and MUC15, and MMP-13 and TIMP3 which has regulatory effects on MMP-13 activity[17-19] in PTC, and to examine their clinicopathological correlations such as invasive and metastatic characteristics.

Ⅱ. MATERIALS AND METHODS

1. Case selection and tissue sample preparation

Tumor specimens were obtained from 10 PTC patients who had undergone total thyroidectomy in the Department of Surgery, Yonsei University College of Medicine, Severance Hospital. The specimens were processed for real time reverse transcription-polymerase chain reaction (RT-PCR). Ten normal thyroid tissues were obtained from each contra-lateral lobe of PTC patients exhibiting apparently normal morphology as a control. Both tumor and normal specimens were stored at -70°C for RT-PCR.

Tissues for immunohistochemistry were randomly selected from 98 PTC patients who had undergone surgery in the same surgery department between 2007 and 2008. These patients included 18 males and 80 females, and the average patient age was 43.4 years. After surgical resection, the specimen were fixed with 10% formalin. A tissue array block was made using tissues from these 98 patients, and immunohistochemical study was conducted using sectioned slides from the tissue array block.

2. Real time quantitative PCR

The expression of *MUC4, MUC15, MMP-13,* and *TIMP-3* was analyzed by RT-PCR. Total RNA from tissues were isolated using TRIzol reagent and 3 μg of total RNA was used to synthesize cDNA (SuperScript III Reverse Transcriptase; Invitrogen, Camarillo, CA, USA), according to the manufacturers' protocols. Residual genomic DNA from the samples was eliminated by DNase I digestion of the RNA preparation. Real-time PCR

amplification for *MUC4* was performed in the presence of double-labeled fluorogenic probe for *MUC4* (*Taq*Man probes; Applied Biosystems, Foster City, CA, USA). A SYBR-Green real time PCR method was used to detect amplification of *MUC15, MMP-13,* and *TIMP-3* using 200Nm primer. Primers for specific *MUC15, MMP-13,* and *TIMP-3* were designed using Primer Express Software (Applied Biosystems (Table 1). Their specificity were confirmed by BLASTIN (www.ncbi.nlm.njh.gov/blast) searches against nucleotide databases. PCR products were sequenced to confirm their identity. Assays were performed using MX3000 (Stratagene, LaJolla, CA, USA). Each experiment was performed in triplicates. The average threshold cycle (C_T) values for GAPDH were used as an internal calibrator to correct for differences in the integrity and the amount of total RNA added to each reaction. For relative quantitation, we used the $2^{-\Delta\Delta C_T}$ method.[20] Results were represented as the mean ± SD of three independent experiments.

Genes	Sequences	bp
MUC15	F: CAACAACAGCCACGGAATAA	97
	R: GGCTTGTGGAAATGGTAGATG	
MMP-13	F:TGGTCCAGGAGATGAAGACC	97
	R: TCCTCGGAGACTGGTAATGG	
TIMP-3	F: ACCTGCCTTGCTTTGTGACT	95
	R: GGCGTAGTGTTTGGACTGGT	

Table 1 Sequences of SYBR-Green real time PCR primers specific to target gene.

3. Tissue microarray and immunohistochemistry

To construct the tissue array block, sections of PTC tissue cores were stained with hematoxylin-eosin to identify areas of tumor tissue and normal tissue. When the areas of interest had been identified, the recipient tissue array block was constructed using manual tissue array equipment (Quick-Ray; UNITMA, Seoul, Korea). We placed 2-mm cores in the recipient block, heated the block to fix the samples into the block, and applied a paraffin layer to ensure proper facing. To facilitate blinded grading, an Excel spreadsheet (Microsoft Corporation, Redmond, WA) was constructed using sample accession numbers but without identifying the final pathological finding.

Sectioned slides were deparaffinized three times in xylene for 20 min each and rehydrated using a graded alcohol solution. Antigen retrieval was performed in 10 mM citrate buffer at pH 6.0 for 10 min in a microwave. Slides were allowed to cool to room temperature and sequentially rinsed three times in PBS and 50 mM Tris-HCl (pH 7.6), 150 mM NaCl, and Tween 20 (0.025%; TBS-T) for 2 min each. Endogenous peroxidase activity was quenched by incubation in peroxidase-blocking reagent (code S2001; DakoCytomation, Carpinteria, CA). Each incubation step was carried out at room temperature, followed by three sequential washes of TBS-T for 5 min each. Sections were incubated in primary antibody diluted in 10% serum (goat serum, Jackson ImmunoResearch Laboratories Inc., West Grove, PA; rabbit and horse serum, Vector Laboratories Inc., Burlingame, CA). The secondary antibody was diluted in antibody diluent (DakoCytomation) and incubated with a biotinylated secondary antibody for 30

min, peroxidase-labeled streptavidin for 20 min (LSAB-2; DakoCytomation), and diaminobenzidine chromogen substrate (DakoCytomation) for 5 min. Slides were counterstained with hematoxylin, dehydrated in a graded alcohol solution, and mounted. The negative controls were incubated with nonimmune IgG of the primary antibody host.

The following antibodies were used in our study: mouse monoclonal MUC4 (1:100, Invitrogen); rabbit polyclonal MUC15 (1:50, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA); mouse monoclonal MMP-13 (1:50, Santa Cruz Biotechnology, Inc.); mouse monoclonal TIMP3 (1:50, Santa Cruz Biotechnology, Inc.)

4. Immunohistological scores and clinicopathological parameters

A surgical pathologist, who was blinded to the identity of the specimens scored them using a semiquantitative scoring system as previously reported.[15,21,22] As shown in Table 2, immunoreactivity was assessed by the percentage of positive cells and intensity of staining, each being scored from 0 to +3. The tumor score was defined as the sum of scores for positivity and for intensity in PTC tissue.

Positivity score	Intensity score
1. Evaluation of immunohistochemistry	
0: 0%	0: no immunoreaction
+1:1-33% positive	+1: weak immunoreaction
+2:34-66% positive	+2: moderate immunoreaction
+3:67-100% positive	+3: strong immunoreaction
2. Tumor score = positivity score + intensity score in tumor	

Table 2 Semiquantitative scoring of MUC4, MUC15, MMP-13 and TIMP-3

On the basis of the clinical and pathologic records, a retrospective analysis was performed on the following variables: age, gender, tumor size, subtype (PTMC; papillary thyroid microcarcinoma, PTC; papillary thyroid carcinoma), lymph node metastasis, extra-capsular invasion, multifocality, distant metastasis, and clinical stage. Clinical stage was determined according to the pTNM system.[23] Immunohistochemical results were correlated with the clinicopathological parameters to evaluate the prognostic significance.

5. Statistical analysis

Scores were expressed as the mean±SD. Statistical analysis was performed using SPSS statistical software (version 13.0, SPSS, Inc., Chicago, IL). Mann-Whitney U test was used to compare the expression level of each gene expression level between PTC and normal tissue. Independent-Samples T test was used to compare average tumor scores of markers and clinicopathological variables. The number of positive immunoreactivities (tumor score>0) in PTC and normal thyroid tissues were evaluated using chi-square test. A P-value less than 0.05 was accepted as a significant difference.

Ⅲ. RESULTS

1. Expression of *MUC4, MUC15, MMP-13,* and *TIMP-3* RNAs in PTC and normal thyroid tissues

To compare gene expression of *MUC4, MUC15, MMP-13,* and *TIMP-3* between PTC and normal thyroid tissues, *MUC4, MUC15, MMP-13,* and *TIMP-3* mRNA expression was analyzed by real time-PCR. As shown in Figure 1, *MUC4*- specific mRNA increased approximately by 78-fold and *MUC15*- specific mRNA by approximately 4.75-fold in PTC compared to normal thyroid tissues. These findings demonstrate that expreesion of membrane mucins, *MUC4* and *MUC15,* was up-regulated in PTC at transcription level. *MMP-13* and *TIMP-3* gene expressions decreased by approximately 0.39-fold and 0.53-fold respectively in PTC compared to normal thyroid tissue (Fig. 1). These findings implicate that *MMP-13* (collagenase) and *TIMP-3* (inhibitor of MMP-13) expressions were down-regulated in PTC at transcription level.

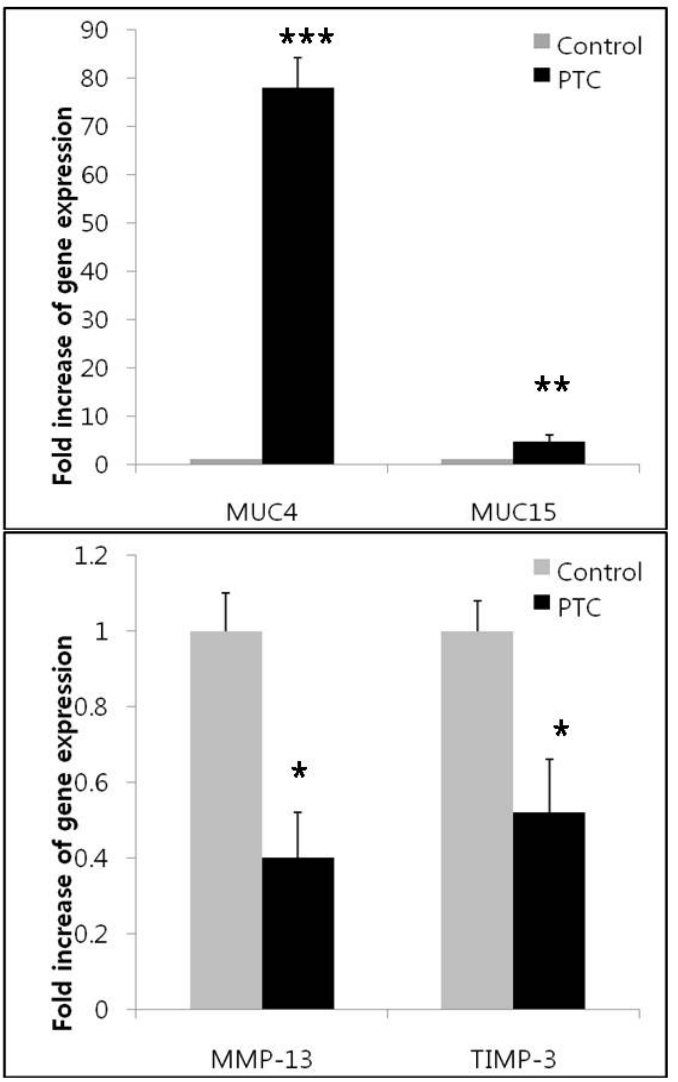

Fig. 1 Real time PCR assay of relative mRNA levels of *MUC4, MUC15, MMP-13,* and *TIMP-3* in PTC and normal thyroid tissues. Quantification data were normalized to the expression of the housekeeping gene GAPDH. The y-axis shows an increase in specific mRNA over unstimulated samples. Data represent the mean ± SD from an experiment done in triplicates; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

2. Immunohistochemical expression in PTC and normal thyroid tissues

To investigate protein expression of MUC4, MUC15, MMP-13, and TIMP-3 between PTC and normal thyroid tissues, tissue-microarrays were constructed. Representative pictures for the expression of MUC4, MUC15, MMP-13, and TIMP-3 are presented in Figure 2 and 3.

In tumor regions, the number of positive immunoreactivities (tumor score>0) was 78 of 98 cases (80%), for MUC4, 97 of 98 (99%) for MUC15, 7 of 98 (7%) for MMP-13, and 8 of 98 (8%) for TIMP-3.

In the non-tumor regions, the number of positive immunoreactivities (tumor score>0) was 10 of 98 cases (10%) for MUC4, 74 of 98 (75%) for MUC15, 48 of 98 (49%) for MMP-13, and 24 of 98 (25%) for TIMP-3 (Table 3).

MUC4 and MUC15 protein expression increased in tumor regions compared to non-tumor regions ($P<0.001$). MMP-13 and TIMP-3 protein expression decreased in tumor regions compared to non-tumor regions ($P<0.001$). Protein expression of MUC4, MUC15, MMP-13, and TIMP-3 corresponded to gene expression levels (Table 4).

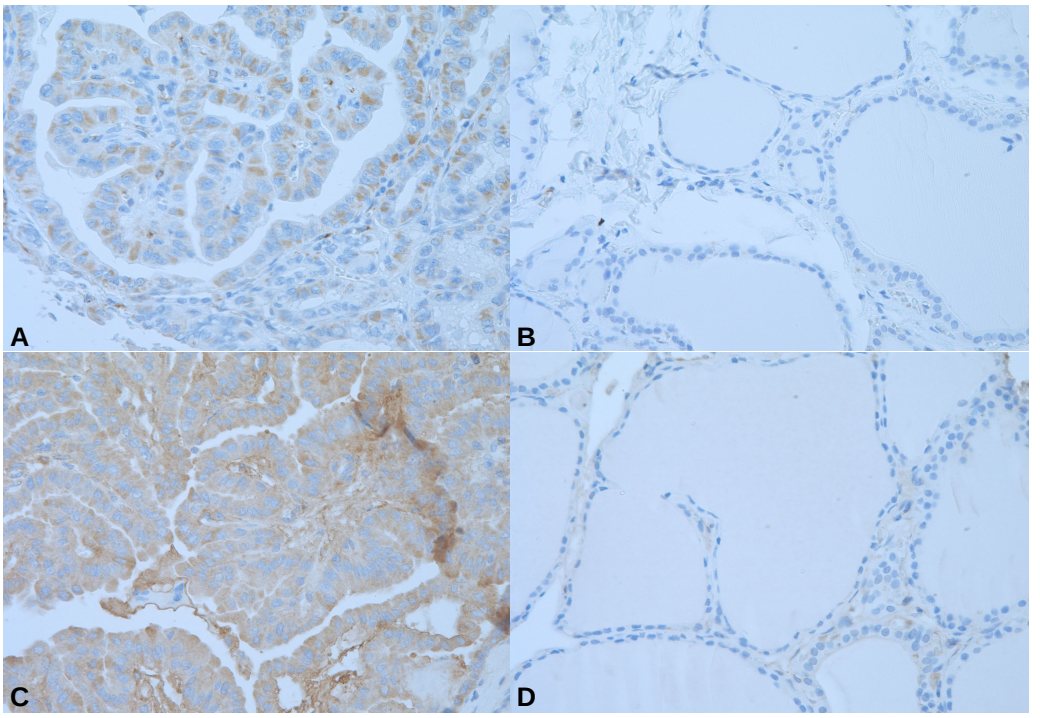

Fig. 2 Immunohistochemical analysis of MUC4 and MUC15 expression in PTC and normal thyroid tissues. MUC4 (**A**) and MUC15 (**C**) are intensely expressed in papillary carcinoma. Normal follicular cells do not express MUC4 (**B**) and MUC15 (**D**) (original magnification, X400).

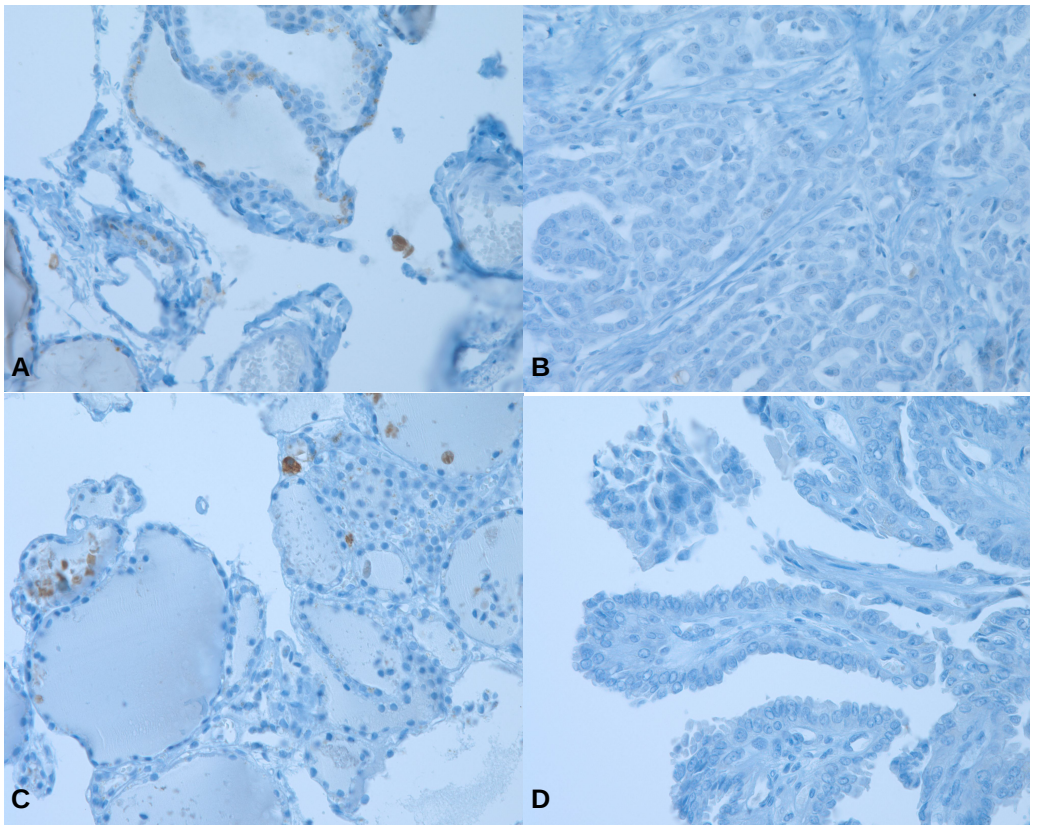

Fig. 3 Immunohistochemical analysis of MMP-13 and TIMP-3 expression in PTC and normal thyroid tissues. MMP-13 (**A**) and TIMP-3 (**C**) are weakly expressed in normal thyroid tissue. Papillary carcinomas do not express MMP-13 (**B**) and TIMP-3 (**D**) (original magnification, X400).

Scores	MUC4	MUC15	MMP-13	TIMP-3
Tumor score				
0	20 (20%)	1 (1%)	91 (93%)	90 (92%)
1-2	4 (4%)	1 (1%)	3 (3%)	1 (1%)
3-4	32 (33%)	9 (9%)	4 (4%)	5 (5%)
5-6	42 (43%)	87 (89%)	0 (0%)	2 (2%)
Non-tumor score				
0	88 (90%)	24 (25%)	50(51%)	73 (75%)
1-2	3 (3%)	23 (24%)	32(33%)	15 (16%)
3-4	7 (7%)	48 (48%)	13(13%)	8 (8%)
5-6	0 (0%)	3 (3%)	3 (3%)	1 (1%)

Table 3 The number (%) of cases according to the tumor/non-tumor scores

Markers	Tissue	Number of positive immunoreactivity (%)	*P*-value
MUC4	Tumor	78 (79.6)	$P < 0.001$
	Non-tumor	10 (10.2)	
MUC15	Tumor	97 (99.0)	$P < 0.001$
	Non-tumor	74 (75.5)	
MMP13	Tumor	7 (7.1)	$P < 0.001$
	Non-tumor	48 (49.0)	
TIMP-3	Tumor	8 (8.2)	$P < 0.001$
	Non-tumor	24 (24.5)	

Table 4 Immunohistochemial analysis of MUC4, MUC15, MMP13 and TIMP-3 expressions in PTC and normal thyroid tissues

3. Correlations between immunohistochemical tumor scores and clinicopathological parameters

The results for the correlation between MUC4 and MUC15 scores and clinicopathological data are shown in Table 5. The MUC4 high scores significantly correlated with small tumor size, and PTMC subtype. The MUC15 high scores significantly correlated with age (≥45 years), presence of distant metastasis, and presence of multifocality. The correlation between MMP 13 and TIMP 3 and clinicopathological data was not analyzed because the number of positive immunoreactivities in tumor region was too small.

	n	MUC4	P value	MUC15	P value
Age (yr)					
< 45	53 (54%)	3.25±2.33	NS	5.40±1.18	
≥ 45	45 (46%)	3.33±1.91		5.80±0.59	*P*=0.032
Gender					
Male	18 (18%)	3.11±2.54	NS	5.83±0.51	NS
Female	80 (82%)	3.89±2.11		5.53±1.04	
Size (cm)					
≤ 2	58 (59%)	4.26±1.98	*P*=0.003	5.53±0.92	NS
> 2	39 (41%)	2.92±2.30		5.64±1.06	
Subtype					
PTMC	38 (39%)	4.32±2.19	*P*=0.034	5.65±0.75	
PTC	60 (61%)	3.35±2.15		5.53±1.10	
LN metastasis					
No	72 (72%)	3.62±2.37	NS	5.62±0.94	NS
Yes	26 (28%)	4.00±1.67		5.46±1.07	
Distant metastasis					
No	88 (90%)	3.74±2.21	NS	5.55±1.02	
Yes	10 (10%)	3.80±2.25		5.90±0.32	*P*=0.021
ECI					
No	72 (72%)	3.75±2.32	NS	5.56±1.04	NS
Yes	26 (28%)	3.65±1.90		5.62±0.80	
Multifocality					
No	64 (65%)	3.54±2.23	NS	5.46±1.11	
Yes	35 (35%)	4.06±2.15		5.79±0.60	*P*=0.048
TNM stage					
I and II	81 (83%)	3.71±2.26	NS	5.58±1.00	NS
III and IV	17 (17%)	3.76±1.99		5.59±0.87	

NS = not significant, PTMC = papillary thyroid microcarcinoma, PTC = papillary thyroid carcinoma, LN = lymph node, ECI = extracapsular invasion

Table 5 Correlation between MUC4 and MUC15 tumor scores and clinicopathological data.

Ⅳ. DISCUSSION

PTC accounts for 80% of thyroid malignancy and is characterized by slow growth and an excellent prognosis.[24] However, 10-15% of cases exhibit aggressive behavior, hallmarked by local invasion, distant metastasis, treatment resistance, and mortality.[25] Although several clinicopathological variables have been identified to assess malignant potential of individual tumors at presentation, none consistently identifies patients at risk for poor outcome. Molecular factors underlying aggressive behavior of PTC may represent more accurate outcome predictors and potential therapeutic targets.

Membrane-associated mucins such as MUC1, MUC4, and MUC15 provide lubrication of epithelial cell surfaces, prevent tissue hydration, and constitute a barrier against infection.[26] They may serve as cell surface receptors and sensors and conduct signals in response to external stimuli that lead to coordinated cellular responses that include proliferation, differentiation, apoptosis, or secretion of specialized cellular products.[27] Cancer cells might use mucins in much the same way as normal epithelia to protect from adverse growth conditions and to control the local microenvironment during invasion and metastasis.

To date, MUC1 overexpression and functional evidence as a key molecular event in the pathogenesis of aggressive PTC are well investigated.[9,10] MUC4 also has been suggested as a biomarker of tumor.[28-30] It can serve as a ligand of receptor tyrosine kinase ErbB2 and modulate cell apoptosis via multiple mechanism.[28] A previous study showed that MUC4 expression was weak and insignificant in thyroid tissues at transcriptional

and protein levels.[12] The limitation of the study was its small population (15 PTC tissues and 22 normal thyroid tissues). However, in our study of 98 patients, *MUC4* gene expression increased by approximately 78-fold in PTC, and MUC4 protein staining scores also significantly increased in PTC compared to normal thyroid tissue. We think using different PCR methods and antibodies may attribute to different results. High expression of MUC4 was associated with small tumor size and papillary thyroid microcarcinoma subtype. We think that MUC4 may play an important role in early oncogenesis of papillary thyroid cancer.

For the first time, our data demonstrated MUC15 protein expression in thyroid gland. Previous studies showed abundant expression of *MUC15* gene in thyroid gland.[31,32] MUC15 is upregulated in colorectal tumors and its expression enhances the oncogenesis potential of colon cancer cells.[33] In our study, *MUC15* gene expression increased by 4.75-fold in PTC, and MUC15 protein staining scores also significantly increased in PTC compared to normal thyroid tissue. Of the 98 tissues, 89% scored 5-6 points in tumor regions but only 3% scored 5-6 points in non-tumor regions. High expression of MUC15 in tumor cells was associated with old age, the presence of distant metastasis, and multifocality. These findings implicate that MUC15 overexpression is associated with aggressive behavior of PTC.

Several studies showed protein expression of MMP and TIMP in thyroid carcinoma, which was first report was that of Campo *et al*. They demonstrated that MMP-2 protein overexpression is associated with tumor invasion and metastasis in thyroid carcinoma.[34] Maeta *et al*. suggested that MMP-2, MMP-9, TIMP-1, and TIMP-3 proteins and

activities increased in tumor cells of PTC, and they play an important role in the invasion and metastasis of PTC.[15] In contrast to other MMPs, Ito *et al*. demonstrated that overexpression of MMP-7 and MMP-11 is inversely linked to aggressive characteristics of PTC, and their downregulation may indicate poor prognosis.[16] Our study was the first to examine MMP-13 and TIMP-3 expressions in PTC. However, MMP-13 and TIMP-3 expressions were downregulated in tumor cells compared to non-tumor thyroid cells. In other tumors such as breast cancer, squamous cell carcinoma of head and neck, and malignant melanoma, MMP-13 was over-expressed in tumor cells, and high expression levels were associated with aggressiveness and poor prognosis. The physiologic significance of MMP-13 and TIMP-3 downregulation in PTC needs to be investigated.

Ⅴ. CONCLUSION

The present study of PTC suggests that membrane mucins, MUC4 and MUC15, are overexpressed in tumor cells, and high levels of MUC15 expression was associated with high malignant potential. MUC15 may serve as a prognostic marker and potential novel therapeutic target in PTC.

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< ABSTRACT(IN KOREAN)>

유두갑상선암에서 MUC4, MUC15, MMP-13 및 TIMP-3 유전자 발현

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남 기 현

유두갑상선암은 가장 흔한 갑상선암 종으로 일반적으로 느린 성장을 보이며 양호한 예후를 보인다. 본 연구에서는 정상 갑상선 조직과 유두 갑상선암 조직에서 막성 점액소인 MUC4와 MUC15의 유전자 발현을 비교하고, MMP 중 아직 밝혀지지 않은 MMP13과 이의 조절 작용을 가지는 TIMP3의 유전자 발현을 비교하고자 한다. 또한 이들의 발현과 임상병리학적 요인들의 상관관계를 알아보고자 한다.

정상 갑상선 조직 (n=10)과 유두 갑상선암 조직 (n=10)에서 리보핵산을 추출하고 MUC4, MUC15, MMP13 및 TIMP3에 대한 실시간 역전사 중합연쇄반응을 시행하였다. 98명의 유두갑상선암 환자의 조직에서 조직배열 블록을 만든 후, 절단된 슬라이드를 이용하여 면역조직화학염색을 시행하였다. 염색의 반정량 점수로 임상병리학적 요인들과의 상관관계를 알아본 후 예후인자로서의 의미가 있는지 알아보았다.

역전사 중합연쇄반응을 시행한 결과, 정상 조직에 비해 유두암 조직에서, MUC4와 MUC15의 특정 리보핵산은 각각 87배와 4.75배가 증가하였고, MMP13과 TIMP3의 유전자 발현은 각각 0.39배와 0.53배로 감소하였다. 면역조직화학염색을 시행한 결과, 정상 조직에 비해 유두암 조직에서, MUC4와 MUC15의 단백질 발현이 증가하였고($P<0.001$), MMP13과 TIMP3은 감소하였다 ($P<0.001$). 임상병리학적 요인들과의 분석결과, 암의 크기가 작은 경우와 미세유두갑상선암에서 MUC4 염색의 반정량 점수가 높았고, 45세 초과인 경우와 원격 전이를 보이는 경우 및 다발성 병변을 보이는 경우에서 MUC15 염색의 반정량 점수가 높았다.

본 연구를 통해서 MUC4와 MUC15가 정상 조직에 비해 유두암 조직에서 과발현되었으며, MUC15의 과발현 정도는 유두암의 악성도와 비례하였다. 따라서 유두갑상선암에서 MUC15이 새로운 예후 인자 및 잠재적인 치료 표적으로 역할을 함 가능성을 제시한다.

핵심되는 말: MUC4, MUC15, MMP-13, 유두갑상선암, TIMP-3, 유전자 발현