Int J Clin Exp Pathol 2015;8(5):5695-5701
www.ijcep.com /ISSN:1936-2625/IJCEP0007173

Original Article

Overexpression of cytokeratin 17 is associated with the development of papillary thyroid carcinoma and the presence of lymph node metastasis

Hyun-Soo Kim[1*], Jeong-Ju Lee[2*], Sung-Im Do[3], Kyungeun Kim[3], In-Gu Do[3], Dong-Hoon Kim[3], Seoung Wan Chae[3], Jin Hee Sohn[3]

[1]Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Pathology, Myongji Hospital, Goyang, Republic of Korea; [3]Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. [*]Equal contributors.

Received February 17, 2015; Accepted April 13, 2015; Epub May 1, 2015; Published May 15, 2015

Abstract: Cytokeratin 17 (CK17), a basal/myoepithelial cell keratin, appears to play an important role in the progression of several human malignancies. Increased CK17 expression has previously described in cases of papillary thyroid carcinoma (PTC). However, no studies to date have investigated the clinical significance of CK17 expression in patients with PTC. The aim of this study was to compare the expression of CK17 in patients with PTC with that observed in normal thyroid tissue and benign thyroid lesions, and to examine the relationship between CK17 expression and clinicopathologic characteristics of patients with PTC. CK17 protein expression was evaluated by immunohistochemistry on tissue microarrays containing thyroid tissue samples from 108 PTCs, 16 nodular goiters, and 81 healthy controls. Sixty-five of the 108 (60.2%) PTC tissue samples exhibited positive CK17 expression, whereas all nodular goiters and normal thyroid tissue samples showed a complete absence of CK17 immunoreactivity. The difference in frequency of CK17 positivity between PTC (65/108, 60.2%), normal thyroid tissue (0/81, 0.0%), and benign thyroid lesions (0/16, 0.0%) was statistically significant (P<0.001). Positive CK17 expression in PTC was significantly associated with the presence of lymph node metastasis (P=0.024) and higher pN stage (P=0.028). Expression of CK17 is significantly increased in cases of PTC compared to normal tissue and benign thyroid lesions, and CK17 overexpression is associated with the presence of lymph node metastasis in patients with PTC. These findings suggest that CK17 is involved in the development and metastasis of PTC.

Keywords: Cytokeratin 17, immunohistochemistry, lymph node metastasis, papillary thyroid carcinoma

Introduction

Papillary thyroid carcinoma (PTC) constitutes 85-90% of all malignant thyroid neoplasm [1, 2]. Generally, PTC is relatively indolent and its long-term outcomes are favorable with a survival rate >90% [1]. However, some PTCs display aggressive features; certain clinicopathologic characteristics such as advanced age, large tumor size, and the presence of extrathyroidal extension or cervical lymph node metastasis have been suggested as poor prognostic factors [3-5]. Similar to other human malignancies, tumorigenesis and progression of PTC are caused by numerous reproductive, environmental, and genetic risk factors. Therefore, it is of great importance to identify the genetic changes and molecular events involved in the initiation, progression, and metastasis of PTC.

Most eukaryotic cells contain cytoskeletal system consisting of intermediate filaments in their cytoplasm. Among the intermediate filaments, keratins are outstanding due to its high molecular diversity. Keratin filament bundles insert at desmosomes at cell-cell contact sites of keratinocytes of the epithelial cells. This feature suggests that keratins play a major functional role in the integrity and mechanical stability of epithelial cell morphology and intercellular feature [6].

Cytokeratins show characteristic expression patterns in epithelial cells according to origin of cell, differentiation, and its role. Cancers fre-

quently retain the expression patterns of cytokeratins that are associated with that particular organ cell type. Thus, cytokeratin profiling provides useful information for detecting the primary site of carcinomas that have metastasized.

Cytokeratin 17 (CK17), regarded as a basal/myoepithelial cell keratin, was originally identified as a major cytokeratin in cutaneous basal cell carcinomas but not in normal epidermis [7]. In normal human epithelia, CK17 expression is observed in the respiratory tract, urinary tract, and various glands [8, 9]. Previous studies have demonstrated that CK17 can be a specific marker of adenocarcinomas of the biliary tract, and that it is a useful for distinguishing pancreatobiliary adenocarcinoma from other adenocarcinomas arising from digestive tract, reproductive tract, lung, and prostate [10-12]. In addition, several studies have shown a significant relationship between CK17 expression and prognosis in patients with gastric adenocarcinoma and ovarian carcinoma [13, 14]. However, the expression patterns and involvement of CK17 in PTC are still unclear, and the clinical significance of CK17 expression in patients with PTC has yet to be investigated.

The aim of this study was to compare the expression of CK17 in cases of PTC with that observed in normal thyroid tissue and benign thyroid lesions, and to examine the relationship between the expression of CK17 and clinicopathologic characteristics of patients with PTC.

Materials and methods

Patients and tissue specimens

We retrospectively reviewed 108 cases of PTC and 16 cases of nodular goiter from records obtained from the Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks were sectioned and stained with hematoxylin and eosin (H&E). The original H&E-stained slides were reviewed by all authors, and a diagnostic consensus was achieved in all cases. For PTC cases, clinicopathologic characteristics including age, gender, size of tumor, multifocality, presence of extrathyroidal extension, lymph node metastasis, and/or distant metastasis, tumor-node-metastasis (TNM) stage, and the presence of a *BRAF* mutation were evaluated by reviewing patient medical records. A total of 81 normal thyroid tissue samples were collected for comparison of immunoreactivity. The Institutional Review Board at Kangbuk Samsung Hospital reviewed and approved this study (2014-01-002).

Construction of tissue microarray

The surgical specimens were fixed in 10% buffered formalin, processed, and embedded in paraffin using a standard protocol. All H&E stained slides were reviewed, and the most representative tumor area was carefully selected and marked on individual FFPE blocks. The most representative tissue core (2 mm diameter) was then obtained from each tumor specimen and was manually arrayed in a recipient paraffin block by two pathologists (S.-I.D. and S.W.C.). The assembly was held in an X-Y position guide with a 1-mm increment between the individual samples, and the instrument was used to create holes in a recipient paraffin block with defined array cores. The fit needle was used to transfer the tissue cores into the recipient block. The percentage of tissue cores containing tumor tissue was greater than 70%. To compare the expression patterns of CK17, 81 samples of normal thyroid tissue were also obtained.

Immunohistochemistry

Immunohistochemical staining was performed on 3 μm-sectioned TMA blocks using a compact polymer method (Bond Intense Detection kit, Leica Biosystems, Newcastle, UK). The sections were deparaffinized and dehydrated using a graded series of ethanol solutions. Endogenous peroxidase activity was halted through incubation with 0.3% hydrogen peroxidase and methanol for 20 min. Following a rinse in phosphate-buffered saline, the tissue sections were processed in a citrate buffer (0.01 M, pH 6.0) inside a heat-resistant plastic container. Sections were then irradiated in a domestic microwave oven for 20 min and allowed to cool at room temperature. The primary antibody used was CK17 (1:200; Dako, Glostrup, Denmark). The sections were incubated with primary antibody overnight at 4°C, followed by the secondary antibody. The negative controls were stained without primary antibody.

Table 1. Expression of CK17 in normal thyroid tissue, nodular goiters and PTC

	No. of patients (%)					*P*-value
	0	1+	2+	3+	4+	
Normal thyroid	81 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001[a*]
Nodular goiter	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001[b*]
PTC	38 (35.2)	5 (4.6)	18 (16.7)	20 (18.5)	27 (25.0)	

[a]PTC versus normal thyroid tissue; [b]PTC versus nodular goiter; [*]Statistically significant.

Immunoreactivity was independently scored by two board-certified pathologists (H.-S.K. and J.-J.L.). Following previous studies, the number of positive cells is quantified as follows: 0, no positive cells present; 1+, scattered positive cells present amounting to less than 1%; 2+, 1-10% of lesional cells positive; 3+, 10-50% of lesional cells positive; 4+, more than 50% of lesional cells positive [15, 16]. When a discrepancy occurred between the two pathologists, the tissue sample was reviewed together for a consensus opinion.

Detection of the BRAF^{V600E} mutation

For the detection of the *BRAF^{V600E}* mutation, nucleic acids from fresh thyroid tissue obtained from patients who had given informed consent were isolated using a DNA extraction kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Briefly, isolated nucleic acids were mixed with a polymerase chain reaction (PCR) master mix from a Seeplex *BRAF^{V600E}* ACE detection kit (Seegene Inc., Seoul, Republic of Korea). The mixed samples were immediately placed in a preheated (94°C) thermal cycler for 15 min, and PCR was carried out using the recommended program in a GeneAmp PCR 9700 system (Applied Biosystems, Foster City, CA, USA). The cycling amplification program consisted of 35 cycles: denaturation for 30 s at 94°C, annealing for 30 s at 63°C, and extension for 1 min at 72°C. The amplified PCR products were loaded onto a 2% agarose gel and were visualized with SafeView Stain (Applied Biological Materials Inc., Richmond, BC, Canada). The *BRAF* mutation was detected with a Gel Documentation system (Bio-Rad Laboratories Inc., Hercules, CA, USA).

Statistical analysis

Pearson's chi-square tests or Fisher's exact tests were performed to compare CK17 expression between normal thyroid tissue, nodular goiters, and PTCs, and to determine whether the status of CK17 expression in PTC is associated with clinicopathologic characteristics including age, gender, size of the tumor, multifocality, presence of extrathyroidal extension or lymph node metastasis, and/or the presence of a BRAF mutation. The linear-by-linear association test was used to examine the relationship between CK17 expression status and pT, pN, and TNM stage. The receiver-operating characteristic curve was generated to divide the data into separate groups to allow for comparisons. Using the receiver-operating characteristic curve analysis, we determined 10% to be the cut-off point for classifying cases into CK17-positive PTCs versus CK17-negative PTCs. Statistical analyses were performed using the SPSS Software Package (version 18.0; IBM SPSS, Chicago, IL, USA). Statistical significance was set at $P<0.05$.

Results

Patient characteristics

The mean age of patients at the time of diagnosis was 42.7 years (range, 23-73). The mean tumor size was 0.95 cm (range, 0.2-5.5 cm), and 79 cases (73.1%) were diagnosed as micropapillary carcinomas. Multifocal PTCs were observed in 25 cases (23.1%). Extrathyroidal tumor extension was noted in 52 cases (48.1%). The pT category distribution was as follows: pT1, 55 (50.9%); pT2, 1 (0.9%); pT3, 52 (48.1%). The pN category distribution was as follows: pN0, 46 (42.6%); pN1a, 54 (50.0%); pN1b, 8 (7.4%). Twenty-eight cases were classified as stage I (75.9%), 72 as stage III (66.7%), and 8 as stage IV (7.4%). *BRAF* mutational analysis was performed in 69 (63.9%) cases, 58 (84.1%) of which were positive.

Expression of CK17 in PTC and its relationship with clinicopathologic characteristics

CK17 immunoreactivity was completely absent in all of the nodular goiter (16.0%) and normal thyroid tissue samples (81.0%). In contrast, 65 of the 108 (60.2%) PTC tissue samples exhibit-

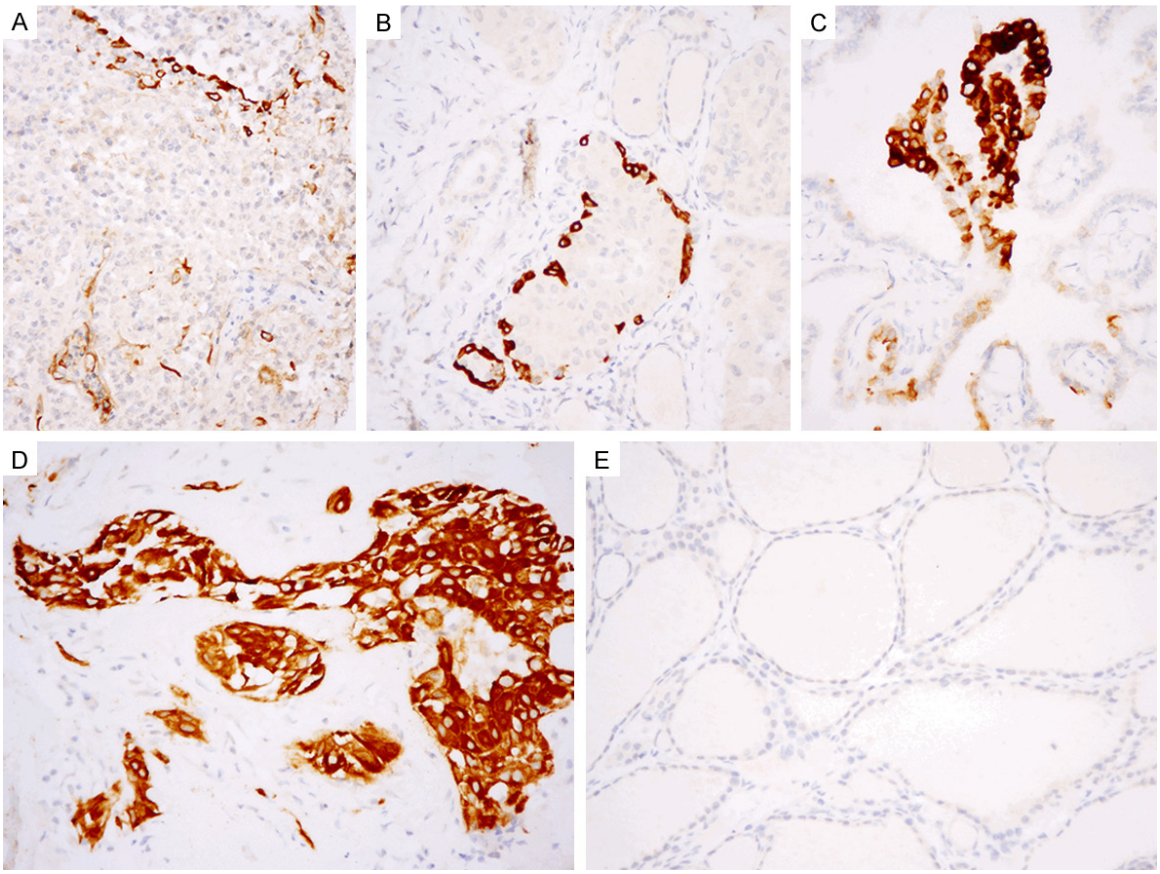

Figure 1. CK17 immunostaining results in PTC (A-D) and nodular goiter (E). The expression was observed in the cytoplasm of tumor cells. (A) Few tumor cells show CK17expression (1+). (B) Less than 10% of PTC cells express CK17 (2+). (C) The tumor cells showing CK17 expression are easily observed but less than 50% (3+). (D) Diffuse strong CK17 expression in PTC (4+). Regardless the expression rate, all CK17 positive cells show storing intensity. (E) None of the nodular goiter cases shows CK17 expression.

ed positive CK17 expression. The difference in frequency of CK17 positivity between PTC and normal and benign thyroid tissues was statistically significant ($P<0.001$; **Table 1**). The expression of CK17 was more frequently detected in neoplastic papillae and individual tumor cells within a desmoplastic stroma (**Figure 1**). In some cases, immunoreactivity was also seen in the tumor cells lining papillary structures within the bulk of the tumor.

The association between CK17 expression and clinicopathologic characteristics of PTC was further analyzed, as shown in **Table 2**. Positive CK17 expression in PTC was significantly associated with the presence of lymph node metastasis ($P=0.024$) and higher pN stage ($P=0.028$).

Discussion

To our knowledge, this is the first study to examine the association of CK17 expression with clinicopathologic characteristics in patients with PTC. Although 2 previous studies have reported CK17 expression in thyroid tissues [15, 16], there is no available data on clinicopathologic associations with CK17 expression in patients with PTC.

CK17 is a low molecular weight keratin that belongs to the acidic type I CK family with a molecular mass of 48 KDa, and its counterpart CK subtype is considered to be K6b [17]. Expression of CK17 has been shown in various normal epithelial cells such as myoepithelial cells, basal cells of transitional and pseudostratified respiratory and urinary tract epithelium, stratified squamous epithelium of skin in early developmental stages, and subsets of hair shaft epithelia [8, 9, 18].

By contrast, in some normal tissues, including thyroid tissue, CK17 expression has been

Table 2. Relationship between CK17 expression and clinicopathologic characteristics of patients with PTC

Characteristics		No. of patients (%)		
		Positive	Negative	*P*-value
Age (years)	≤45	43 (62.3)	26 (37.7)	0.547[a]
	>45	22 (53.4)	17 (46.6)	
Gender	Man	23 (67.6)	11 (32.4)	0.283[a]
	Woman	42 (56.8)	32 (43.2)	
Size of tumor (cm)	≤1.0	47 (59.5)	32 (40.5)	0.809[a]
	>1.0	18 (62.1)	11 (37.9)	
Multifocality	Multiple	16 (64.0)	9 (36.0)	0.657[a]
	Single	49 (59.0)	34 (41.0)	
Extrathyroidal extension	Present	34 (65.4)	18 (34.6)	0.287[a]
	Absent	31 (55.4)	25 (44.6)	
Lymph node metastasis	Present	43 (69.4)	19 (30.6)	0.024[a*]
	Absent	22 (47.8)	24 (52.2)	
Distant metastasis	Present	6 (75.0)	2 (25.0)	0.473[a]
	Absent	59 (59.0)	41 (41.0)	
pT stage	pT1	30 (54.5)	25 (45.5)	0.254[b]
	pT2	1 (100.0)	0 (0.0)	
	pT3	34 (65.4)	18 (34.6)	
pN stage	pN0	22 (47.8)	24 (52.2)	0.028[b*]
	pN1a	37 (68.5)	17 (31.5)	
	pN1b	6 (75.0)	2 (35.0)	
TNM stage group	I-II	13 (46.4)	15 (53.6)	0.084[a]
	III-IV	52 (65.0)	28 (35.0)	
BRAF mutation	Present	33 (56.9)	25 (43.1)	0.680[a]
	Absent	7 (63.6)	4 (36.4)	

[a]Chi-square test or Fisher's exact test; [b]Linear-by-linear association test; [*]Statistically significant.

reported to be absent. Chu et al. reported no CK17 expression in normal thyroid tissue, and Yang et al. showed CK17 expression in pancreatobiliary carcinomas but no CK17 expression in normal pancreatobilary cells or normal thyroid follicular cells [19, 20]. Consistent with previous data, we demonstrated an absence of CK17 expression in normal thyroid tissue samples. Instead, we observed significantly increased CK17 immunoreactivity in PTC compared to normal follicular cells. This finding was similar to a previous study that showed no CK17 mRNA in normal oral squamous epithelium, but significant up-regulation of CK17 mRNA in oral squamous cell carcinoma [21]. Another study showed no CK17 expression in normal oral mucosa, and 100% positivity in carcinoma *in situ* and squamous cell carcinoma [22]. In addition, Ide et al. reported 49.5% positivity of CK17 in cases of gastric carcinoma but not in normal gastric mucosa, and Wang et al. reported a significantly higher level of CK17 mRNA and protein expression in ovarian epithelial cancers compared with noncancerous tissues [13, 14]. Finally, Guelstein et al. demonstrated CK17 positivity in all urothelial carcinomas examined in their study, in contrast to the negative expression observed in normal urothelium [13, 14, 23].

Recently, CK17 has been shown to participate in cell growth and sizing of keratinocytes by regulating protein synthesis. Cell growth is concomitantly stimulated after serum-dependent cytoplasmic translocation of 14-3-3γ from the nucleus, which requires mammalian rapamycin (mTOR) activity and two amino acid residues located in the N-terminal head domain of CK17. In response to DNA damage, 14-3-3γ has been primarily regarded as a potential tumor suppressor gene that is upregulated by p53. However, its role in the Akt/mTOR signal activation seems to be related to malignant changes in the tissue [24, 25].

We also found a significant association between CK17 expression and the presence of lymph node metastasis as well as a higher pN stage. There have been several studies showing a significant relationship between CK17 expression and poor prognosis in cases of gastric carcinoma, epithelial ovarian carcinoma, and oral squamous cell carcinoma [13, 14, 22]. In addition, CK17 has been correlated with poor histological differentiation, short overall and disease-free survival in invasive ductal carcinomas, and adverse effects on overall and disease-free survival in triple-negative breast cancer [26, 27].

Chang et al. showed that downregulation of CK17 gene expression in keratinocytes using RNAi and antisense technology may be an effective treatment option for patients with psoriasis [28]. Further evaluation is required to verify whether inhibition of CK17 can be used as a therapeutic option in malignant tumors that exhibit CK17 overexpression, as well as to characterize the functional role of CK17 in tumor progression.

In conclusion, we demonstrated that expression of CK17 is significantly increased in cases of PTC compared to normal and benign thyroid tissues, and that CK17 overexpression is associated with the presence of lymph node metastasis and advanced N stage. These findings suggest that CK17 plays an important role in the development and metastasis of PTC.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hyun-Soo Kim, Department of Pathology, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel: +82-2-2228-2648; Fax: +82-2-2227-7939; E-mail: hyunsookim@yuhs.ac; Dr. Sung-Im Do, Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 110-746, Republic of Korea. Tel: +82-2-2001-2393; Fax: +82-2-2001-2398; E-mail: sungim.do@samsung.com

References

[1] Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, Shah JP, Fremgen AM, Stewart AK and Holzer S. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. Cancer 2000; 89: 202-217.

[2] Davies L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006; 295: 2164-2167.

[3] Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J Surg 2007; 31: 2085-2091.

[4] Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, Gardini G, Valcavi R and Barbieri V. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. Thyroid 2009; 19: 707-716.

[5] Moreno-Egea A, Rodriguez-Gonzalez JM, Sola-Perez J, Soria-Cogollos T and Parrilla-Paricio P. Multivariate analysis of histopathological features as prognostic factors in patients with papillary thyroid carcinoma. Br J Surg 1995; 82: 1092-1094.

[6] Moll R, Divo M and Langbein L. The human keratins: biology and pathology. Histochem Cell Biol 2008; 129: 705-733.

[7] Moll R, Franke WW, Volc-Platzer B and Krepler R. Different keratin polypeptides in epidermis and other epithelia of human skin: a specific cytokeratin of molecular weight 46,000 in epithelia of the pilosebaceous tract and basal cell epitheliomas. J Cell Biol 1982; 95: 285-295.

[8] Troyanovsky SM, Guelstein VI, Tchipysheva TA, Krutovskikh VA and Bannikov GA. Patterns of expression of keratin 17 in human epithelia: dependency on cell position. J Cell Sci 1989; 93: 419-426.

[9] Troyanovsky SM, Leube RE and Franke WW. Characterization of the human gene encoding cytokeratin 17 and its expression pattern. Eur J Cell Biol 1992; 59: 127-137.

[10] Chu PG, Schwarz RE, Lau SK, Yen Y and Weiss LM. Immunohistochemical staining in the diagnosis of pancreatobiliary and ampulla of Vater adenocarcinoma: application of CDX2, CK17, MUC1, and MUC2. Am J Surg Pathol 2005; 29: 359-367.

[11] Goldstein NS and Bassi D. Cytokeratins 7, 17, and 20 reactivity in pancreatic and ampulla of vater adenocarcinomas. Percentage of positivity and distribution is affected by the cut-point threshold. Am J Clin Pathol 2001; 115: 695-702.

[12] Miettinen M NM, Tuma BT. Keratin 17: immunohistochemical mapping of its distrubution in human epithelial tumors and its potential applications. Appl Immunohistochem 1997; 152-159.

[13] Ide M, Kato T, Ogata K, Mochiki E, Kuwano H and Oyama T. Keratin 17 expression correlates with tumor progression and poor prognosis in gastric adenocarcinoma. Ann Surg Oncol 2012; 19: 3506-3514.

[14] Wang YF, Lang HY, Yuan J, Wang J, Wang R, Zhang XH, Zhang J, Zhao T, Li YR, Liu JY, Zeng LH and Guo GZ. Overexpression of keratin 17 is associated with poor prognosis in epithelial ovarian cancer. Tumour Biol 2013; 34: 1685-1689.

[15] Baloch ZW, Abraham S, Roberts S and LiVolsi VA. Differential expression of cytokeratins in follicular variant of papillary carcinoma: an immunohistochemical study and its diagnostic utility. Hum Pathol 1999; 30: 1166-1171.

[16] Miettinen M, Kovatich AJ and Karkkainen P. Keratin subsets in papillary and follicular thyroid lesions. A paraffin section analysis with diagnostic implications. Virchows Arch 1997; 431: 407-413.

[17] Smith FJ, Jonkman MF, van Goor H, Coleman CM, Covello SP, Uitto J and McLean WH. A mutation in human keratin K6b produces a phenocopy of the K17 disorder pachyonychia congenita type 2. Hum Mol Genet 1998; 7: 1143-1148.
[18] Chu PG and Weiss LM. Keratin expression in human tissues and neoplasms. Histopathology 2002; 40: 403-439.
[19] Chu PG, Lau SK and Weiss LM. Keratin expression in endocrine organs and their neoplasms. Endocr Pathol 2009; 20: 1-10.
[20] Yang HS, Tamayo R, Almonte M, Horten B, DaSilva M, Gangi M, Vazquez E, Joseph D, Okamoto P and Scholl T. Clinical significance of MUC1, MUC2 and CK17 expression patterns for diagnosis of pancreatobiliary arcinoma. Biotech Histochem 2012; 87: 126-132.
[21] Mikami T, Cheng J, Maruyama S, Kobayashi T, Funayama A, Yamazaki M, Adeola HA, Wu L, Shingaki S, Saito C and Saku T. Emergence of keratin 17 vs. loss of keratin 13: their reciprocal immunohistochemical profiles in oral carcinoma in situ. Oral Oncol 2011; 47: 497-503.
[22] Toyoshima T, Vairaktaris E, Nkenke E, Schlegel KA, Neukam FW and Ries J. Cytokeratin 17 mRNA expression has potential for diagnostic marker of oral squamous cell carcinoma. J Cancer Res Clin Oncol 2008; 134: 515-521.
[23] Guelstein VI, Tchipysheva TA, Ermilova VD and Troyanovsky SM. Immunohistochemical localization of cytokeratin 17 in transitional cell carcinomas of the human urinary tract. Virchows Arch B Cell Pathol Incl Mol Pathol 1993; 64: 1-5.
[24] Kim S, Wong P and Coulombe PA. A keratin cytoskeletal protein regulates protein synthesis and epithelial cell growth. Nature 2006; 441: 362-365.
[25] Yang HY, Wen YY, Chen CH, Lozano G and Lee MH. 14-3-3 sigma positively regulates p53 and suppresses tumor growth. Mol Cell Biol 2003; 23: 7096-7107.
[26] Malzahn K, Mitze M, Thoenes M and Moll R. Biological and prognostic significance of stratified epithelial cytokeratins in infiltrating ductal breast carcinomas. Virchows Arch 1998; 433: 119-129.
[27] Thike AA, Iqbal J, Cheok PY, Chong AP, Tse GM, Tan B, Tan P, Wong NS and Tan PH. Triple negative breast cancer: outcome correlation with immunohistochemical detection of basal markers. Am J Surg Pathol 2010; 34: 956-964.
[28] Chang T, Sun L, Wang Y, Wang D, Li W, Li C, Gao T, Liu Y and Wang G. Inhibition of keratin 17 expression with antisense and RNAi strategies: exploring novel therapy for psoriasis. Exp Dermatol 2011; 20: 555-560.