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Original Article

Immunohistological expression patterns of cytokeratin subtypes in both normal and malignant tissues

－Review of previous articles and our additional study to establish the discriminating table for metastatic carcinomas of unknown origin－

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Objective: Cytokeratins (CK) was classified into 20 subtypes, and each cell revealed specific CK subtypes regardless of benignancy or malignant transformation. Because either CK7 (type II, 54kD) or CK20 (type I, 46kD) was found microscopically in most simple epithelia or carcinomas, the immunohistological expression pattern of CK7 and CK20 was used to confirm the primary organ of metastatic carcinomas.

Study design and Results: In this article, the constitution and expression patterns of CK7 and CK20 were reviewed from previous reports and supplemented by our additional study to complete our routine immunohistological CK discrimination table for tissue origin.

Conclusion: As to several metastatic carcinomas, their correct origin could be immunohistologically pointed out according to CK7/CK20 expression patterns.

Key Words: cytokeratin 7, cytokeratin 20, immunohistology

Introduction

Intracytoplasmic cytoskeletons were composed of actin of microfilaments, tubulin of microtubules, and intermediate filaments (IFs). IFs consisted of desmin, vimentin, glial fibrous acidic protein (GFAP), neurofilament (NF), and (cyto-) keratin (CK). CKs were generally classified into type I (high molecular basic type) and type II (low molecular acidic type), and, furthermore, consisted of 20 subtypes (Moll's classification), from the subtype CK1 of the most highest molecular weight to the subtype CK20 of the lowest molecular weight. (Table 1) 5) Each subtype of type I CKs was paired with a specific type II subtype, which was defined microscopically by co-expression. Any cell could not synthesize all subtypes of CK simultaneously, but specific subsets of CKs were expressed in different circumferences and in different organ epithelia. Thus, most epithelia and their related carcinomas could be classified microscopically on the basis of an expression of CK subtypes. Because their expression patterns of CK subtypes had been preserved under malignant transformation, primary organs were easily indicated by the immunohistological CK analysis of metastatic tissues. 1-5)

Materials and methods

Our examined cases were listed in Table 2 and Table 3.

The 10%-neutral-formalin-fixed and paraffin-embedded tissue-blocks were used.

Immunohistological staining was done according to our text.5) Primary antibodies against CK7 and CK20 were delivered from DAKO Company (DAKO・JAPAN Co., Kyoto). Their antigenicity was retrieved with the pretreatment by a microwave oven just before immunostaining procedure.5)

Positive patterns of CKs subtypes were classified into four groups as follows: (1) CK7+/CK20+; both CK subtypes were exhibited, (2) CK7+/CK20-; only CK7 was confirmed, (3) CK7-/20+; only CK20 was positive, (4) CK7-/CK20; no staining was found.

Results

CK stainability was sufficient to confirm microscopically under a low power view analysis. The staining positivity in normal tissues was listed in Table 2. The staining result in various malignant tissues was also listed in Table 3. The reviewed reference data were abbreviated as C, H, T, and W in Tables in the same manner as our data. 1-5)

Discussion

CK7 and CK20 were exhibited in most epithelia regardless of their malignant transformation, and their specific exhibition patterns allowed to confirm primary foci in histological analyses of metastatic tissues. 1-5) Our additional data completed our CK discriminat-

ing table, including reviewed data.

Reference

1. Chu PG, et al. Review. Keratin expresson in human tissues and neoplasms. Histopathology 2002;40:403-19.
2. Heatley MK. Correspondence. Keratin expression in human tissues and neoplasms. Histopathology 2002;41:365-6.
3. Taniere P, et al. Cytokeratin expression in adenocarcinomas of the esophagogastric junction, a comparative study of adenocarcinomas of the distal esophagus and of the proximal stomach. Am J Surg Pathol 2002;26:1213-21.
4. Wang NP, et al. Coordinate expression of cytokeratins 7 and 20 defines unique subsets of carcinomas. Appl Immunohistochem 1995;3:99-107.
5. Immunohistochemistry and PCR. In: Ikarashi T, editor. Obstetrical and Gynecological Pathology ABC - Clinicopathological mechanism and its medical strategy-. 34th ed. Nagaoka: Pimento Press; 2002. (Softs: Windows, Exel, PowerPoint (Microsoft), Photoshop (Adobe), Ichitaroh (Justsystem), and DocuWorks Desk (Fuji Xerox), total contents of 26.5GB)

和 文 抄 録

原著

正常および悪性組織におけるサイトケラチン亜型の免疫組織学的発現パターン－文献的考察と追加実験による再検討による原発巣推定鑑別表の作成－

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目的：細胞骨格を構成する中間型フィラメントであるサイトケラチン（CKs）は20亜型に分類され、いかなる細胞もその悪性変化にかかわらず特異なCK亜型の組み合わせを発現する。特に、CK7（Ⅱ型、54kD）とCK20（Ⅱ型、46kD）は、大半の単純型上皮に発現することが報告されており、その二種類の免疫組織学的発現の組み合わせ様式は、転移性癌組織の原発巣を推定する為に極めて有用である。この論文では、既報論文におけるCK7とCK20の免疫組織学的発現パターンを再検討し、さらに、追加実験を加え、日常業務に有用な転移性癌の原発巣推定の為の鑑別表を作成することを目的とした。

方法：ホルマリン固定、パラフィン包埋切片について、良悪性と全臓器について、そのCK7とCK20について、免疫染色を実施した。

成績・結論：CK7とCK20の染色性により4グループに分類され、今後の転移巣の原発推量に有意義であることが再確認された。

キーワード：サイトケラチン7，サイトケラチン20、免疫組織病理学

Table 1　Cytokeratin subtypes and their expression in simple and stratified epithelia (reviewed)

abcd	Type II, #Moll (kD, isoelectric point)	Type I, #Moll (kD, isoelectric point)	epidermis	squamous	gland: epithelium	gland: basal cells in two-cell-layer	simple epithelium	others
suprabasal cells	#1 (67, 7.8)	#10 (56.5, 5.3)	entire suprabasal					suprabasal cells of stratified and cornified epithelia
		#11 (56, 5.3)	entire suprabasal					
		#9 (64, 5.4)	palm, sole					
	#2e (65, 6.1)		high layers					late suprabasal cells of stratified cornified epithelia
	#2p (65, 6.1)			gingiva, hard palate				

	Type II, #Moll (kD, isoelectric point)	Type I, #Moll (kD, isoelectric point)	epidermis	squamous	gland: epithelium	gland: basal cells in two-cell-layer	simple epithelium	others
—	#3 (64, 7.5)	#12 (55, 4.9)		cornea				cornea-specific
	#4 (59, 7.3)	#13 (51, 5.1)		non-keratinizing of internal organ				mucosa and non-cornified stratified epithelia
	#6 (56, 7.8)	#16 (48, 5.1)	hyperproliferation (wound healing), palmoplantar, appendage	mucosa				
		#17 (46, 5.1)	appendage					most typically expressed in basal cells of complex epithelia
stratified squamous epithelia	#5 (58, 7.4)	#14 (50, 5.3)	basal	basal	epithelia			myoepithelium, mesothelium
		#15 (50, 4.9)		basal				
	#8 (52, 6.1)	#18 (45, 5.7)		non-cornifying				
		#19 (40, 5.2)	appendage	non-cornifying			+	
	#9 (64, 5.4)		palm,sole					
simple epithelia	#7 (54, 6.0)	#19 (40, 5.2)			basal	basal	ductal epithelia (bile duct, pancreatic duct, renal collecting duct), GI epithelia	myoepithelium
		#20 (46, 5.7)					GI epithelia (#7absent)	Merkel, taste bud

	Type II, #Moll (kD, isoelectric point)	Type I, #Moll (kD, isoelectric point)	epidermis	squamous	gland: epithelium	gland: basal cells in two-cell-layer	simple epithelium	others
	#8 (52, 6.1)	#18 (45, 5.7)					+	most secretory and parenchymatous cells

classification basis (Moll, 1982)

1 #: #1 (67kD) ～ #20 (46kD)
2 acid keratin and basic keratin were paired
3 basic kD=acidic kD + 8kD, paired
4 gene of basic keratin: 12q11-13
gene of acidic keratin: 17q12-21
5 each keratin was produced not degradngly but individually

GI gastrointestinal tract

Table 2　Cytokeratin subtype expression patterns in normal organs and tissues

organ		cytokeratin subtype patterns				reference, supplement
	subtype	7+,20+	7+,20-	7-,20+	7-,20-	
bile duct	bile duct	-	+	-	-	B, H02-14146
breast	ductal	-	+	-	-	B
colon	deep	-	-	-	+	B, BH01-12034
colon	surface	-	-	+	-	B, BH01-12034
duodenum	Brunner	-	+ (collecting ductule)	-	-	B, H02-15624
duodenum	villi	+ (CD7: few)	-	++	-	B, H02-15624
epipharynx	respiratory	-	+	-	-	B, B02-14861
esophagus	squamous	-	-	-	+	B, H02-14141
gallbladder	epithelum	-	+	-	-	B, H02-14146
intestine	intestine	-	-	+	-	B
kidney	collecting	-	+	-	-	B, SN02-059
kidney	pelvis, transitinal	+ (CD7: umbrella+basal cell ++, CD20: umbrella only)	-	-	-	B, SN02-059
kidney	distal	-	+, (-)	-	-, (+)	B, 02-13306-1, SN02-059
kidney	glomerulus	-	-	-	+	B, SN02-059
kidney	Henle	-	+	-	-	B, 02-13306-1, SN02-059
kidney	proximal tubule	-	- (+)	-	+	B, 02-13306-1, SN02-059
liver	hepatic ell	-	-	-	+	B
lung	alveolar	-	+	-	-	B, 02-13212-4
lung	bronchial	-	+	-	-	B, 02-13212-4
pancreas	ductal	-	+	-	-	B
pancreas	endocrine	-	-	-	+	B

organ		cytokeratin subtype patterns				reference, supplement
pancreas	exocrine	-	- (+)	-	+	B
prostate	epithelum	-	-	-	+100	B, 20 cases$
prostate	myoepithelium	-	+100, weak in BPH	-	-	B, 20 cases$
stomach	deep, fundic gland	-	-	-	+	B, H02-13721, H02-15624
stomach	deep, pyloric gland	-	+ (few)	-	-	B, H02-1372, H02-156241
stomach	foveola	+ (CD7: weak)	-	-	-	B, H02-13721, H02-15624
stomach	intestinal metaplasia	+ (CD7: weak)	-	-	-	B, H02-13721, H02-15624
thyroid	follicle	-	+	-	-	B
urinary bladder	trasitional	+ (CD7: umbrella+basal cell ++, CD20: umbrella only)	-	-	-	B, carcinoma: CD20+
urinary bladder	trasitional	-	+	-	-	B, 02-14908
uterus, cervix	squamous	-	-	-	+	B, 02-13210-1
uterus, cevix	endocercial	-	+	-	-	B, 02-13210-1
uterus, corpus	endometrial	-	+	-	-	B

abbreviation

B data from Koseiren-Byori-Center, our data, B-, H-, SN-: registered tissue numbers

C data from Chu PG et al. Review. Keratin expresson in human tissues and neoplasms. Histopathology 2002;40:403-19.

W data from Wang NP et al. Coordinate expression of cytokeratins 7 and 20 defines unique subsets of carcinomas. Appl Immunohistochem 1995;3:99-107.

++ strongly positive

+ positive

± weakly positive

- negative

* not analyzed

number % positive cases

BPH benign prostatic hyperplasia

$ 02-15644, 15741, 16277, 16363, 15150, 15241, 15242, 15243, 16013, 16190, 16315, 15185, 15611, 15644, 15734, 15765, 16014, 15243

Table 3 Cytokeratin subtype expression patterns in malignant organs and tissues

organ		cytokeratin subtype patterns				reference, supplement
	subtype	7+,20+	7+,20-	7-,20+	7-,20-	
adrenal	crotical	-0	-0	-0	+100	C
bile duct	mucinous	-	+	-	-	B, H02-14146
breast	adeno	-	+	-	-	W
breast	ductal	-10	+86	-2	-2	C
breast	ductal	-	+	-	-	B
breast	lobular	-6	+94	-0	-0	C
colon	adeno	-	-	+	-	W

organ		cytokeratin subtype patterns				reference, supplement
colon	adeno	-	-	+ (7+: 27, 20+: 94)	-	H
colon	tubular	-8	-0	+82	-10	C
colon	tubular	-	-	+	-	B, 02-13212-4, 01-16942-2, 02-14908
colon	tubular	+ (CK7+, CD20 focally+)	-	-	-	B, H01-12034
esophagus	squamous	-0	+21	-0	+79	C
esophagus, distal	adeno	-15	+74	-2	-8	T
gastrointestinal	carcinoid	-0	-13	-7	+80	C
germ	germ	-0	-7	-0	+93	C
head, neck	squamous	-0	+27	-6	+67	C
kidney	renal cell	-0	-17	-3	+80	C
kidney	renal cell	-	-	-	+ (7+: 11, 20+: 2)	H
kidney	renal cell	-	-	-	+	W
kidney	renal cell, granular	-	+	-	-	B, 02-13306-1
liver	cholangio	+65	+28	-5	-2	C
liver	hepatic cell	-5	-15	-2	+78	C
liver	hepatic cell	-	-	-	+	W
lung	adeno	-10	+90	-0	-0	C
lung	adeno	-	+	-	-	W, B02-14877
lung	carcinoid	-0	+22	-0	+78	C
lung	squamous	-0	+26	-4	+70	C
mesothelium	epithelial	-	+	-	-	W
mesothelium	mesothelioma	-0	+67	-0	+33	C
ovary	mucinous	+	-	-	-	W
ovary	mucinous	+ (7+: 97, 20+: 61)	-	-	-	H
ovary	non-mucinous	-	+ (7+: 96, 20+: 13)	-0	-0	H
ovary	non-mucinous	-2	+98	-0	-0	C
ovary	adeno	-	+ (7+: 100, 20+: 13)	-	-	H
Paget	Paget	-	+	-	-	
pancreas	ductal	+64	+28	-5	-2	C
pancreas	ductal	+	-	-	-	W
pancreas	ductal	+ (CD20:±)	-	-	-	B, 01-2255
pancreas	mucinous	+ (CD20 focal)	-	-	-	B, 01-13701
pancreas	serous	-	+	-	-	B, 01-2813
prostate	adeno	-3	-3	-10	+84	C
prostate	adeno	-	-	-	+	W
prostate	adeno	-13 (focal)	-	-13 (focal)	+75	B, 20 cases$
prostate	mucinous	-	-	(+)	(+)	B, 02-11592-LLM, 02-15644
salivary	ductal	-0	+100	-0	-0	C
skin	Merkel	-0	-0	+78	-12	C
soft tissue	epithelioid sarcoma	-0	-0	-0	+100	C
stomach	adeno	+32	-19	+35	-14	C

organ		cytokeratin subtype patterns				reference, supplement
stomach	adeno	+ (7+: 52, 20+: 63)	-	-	-	H
stomach	carcinoid	-	+	-	-	B, SN02-062
stomach, distal (pyloric)	adeno	-8	-8	+48	+32	T
stomach, proximal	adeno	-19	+24	+36	+21	T
thymus	thymoma	-0	-0	-0	+100	C
thymus	thymoma	-	+	-	-	W
thyroid	thyroid	-0	+98	-0	-2	C
urinary bladder	transitional	+65	+37	+30	-10	C, CD+ in malignancy
urinary bladder	transitional	+	-	-	-	W, CD+ in malignancy
uterus, cervix	adeno, mucinous, endocervical	-	-	+	-	B, 02-13210-1
uterus, cervix	squamous	-0	+87	-0	-13	C
uterus, cervix	squamous	*	+ 87	*	*	H
uterus, corpus	endometrial	-9	+86	-0	-6	C
uterus, corpus	endometrial	-	+ (7+ 96, 20+: 2)	-	-	H
uterus, corpus	endometrial	-	+	-	-	W
uterus, corpus	endometrial	-	+	-	-	B
z, others	neuroendocrine	-0	+56	-0	+44	C
z, others	neuroendocrine	-	-	-	+	W
z, others	small cell	-	-	-	+	W
z, others	squamous	-	-	-	+	W

abbreviation

B data from Koseiren-Byori-Center, our data, B-, H-, SN-: registered tissue numbers

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