

Cyclin A Ki- 67

=Abstract=

Expression of Cyclin A and Ki- 67 in the Uterine Cervical Carcinoma.

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The cell cycle is the set of events that is responsible for the duplication of the cells. Recent studies indicate that cell cycle regulatory proteins, mainly the cyclins and cyclin-related genes, can be critical targets during oncogenesis. The genes and gene products normally control specific events in the cell cycles, particularly during the late G1 and early S phase and G2/M phase. A large body of data implicates cyclins in oncogenesis. The first evidence came from human cyclin A in oncogenesis. Cyclin A is expressed from the late G1 phase through the M-phase of the cell cycle. Cyclin A is known as positive regulator of cell cycle and participates in the tumorigenesis. Overexpression of cyclin A has been reported in several cancers.

Ki-67 is a nuclear protein expressed during the cell cycle except in G₀. The labeling index of Ki-67 in the tumor cell nuclei has been used as a good prognostic factor.

In this study, we compared labeling index of cyclin A and Ki-67 to assess the feasibility between them with 30 cases of cervical intraepithelial neoplasia(CIN) and 20 cases of invasive squamous cell carcinoma(SCC)by immunohistochemistry.

The results were as follow;

1. Cyclin A expressed in normal parabasal cells and their labeling index was $0.8 \pm 0.4\%$, while in CIN and invasive SCC $65.5 \pm 9.4\%$ and $86.5 \pm 12.3\%$ respectively. Ki-67 expressed in normal parabasal cells as $1.3 \pm 0.7\%$ while in CIN and invasive SCC as $77.8 \pm 12.9\%$ and $92.2 \pm 17.6\%$ respectively.

2. In CIN, the expression of cyclin A increased according to the grades of the CIN as $32.5 \pm 5.7\%$, $75.8 \pm 9.0\%$, and $83.2 \pm 13.4\%$ in CIN I, II and III respectively. The expression of the Ki-67 also increased according to the grades of the CIN as $51.8 \pm 9.8\%$, $87.9 \pm 11.3\%$, and $93.6 \pm 17.5\%$ respectively in CIN I, II and III.

3. There was no differences of cyclin A and Ki-67 expressions according to the histologic types of invasive SCC.

Above results suggests that the cyclin A labeling index could be used as a marker of tumor progression in the uterine cervical carcinoma as Ki-67.

Key word: CIN, Cyclin, SCC, Ki-67

I.

가

(cell cycle)

cyclin

1) Cyclin

cyclin A

가

DNA

cyclin A

가 B

가

cyclin A

B

(hybrid protein)

cyclin dependent kinase

(CDK)

S

G2/M

DNA

가

cyclin A

(leukemic cell line)5

cyclin A

6.

7)

Ki-67

Go

(cell fraction)

Ki-67

(labeling

89),

index)

10,

11)

12)

cyclin A

Ki-67

가

(CIN: cervical intraepithelial neoplasia) 30

20

cyclin A

Ki-67

50

21

65

47

가

10

10% buffered formalin

8

14

paraffin

4-6 μ m

hematoxylin-eosin

50

30

가

20

가

CIN I, CIN II

CIN III가

9, 8,

13

20

keratinizing type, large cell nonkeratinizing type,

intermediate cell type

small cell type

3, 8,

7

2

Cyclin A

Ki-67(MIB-1)

Novocas-

tra(UK)

Dako(Denmark)

(indirect)

para-

ffin

xylene

graded alcohol

0.01M citrate buffer(pH 6.0)

microwave

700W

10

peroxidase

methanols(0.03% hydrogen peroxide)

30

10%

가

30

10% BSA(bovine

serum albumin)

PBS(phosphate buffered saline, pH

7.4)

(cyclin A, 1:200 Ki-67: 1:100)

40

PBS

3

biotin

antimouse

rabbit

30

3

PBS

pero-

xidase가

streptavidin

30

PBS

0.05%

3'-3

- Cyclin A Ki-67 -

diaminobenzidine(DAB) normal squamous epithelium of the uterine
hematoxylin cervix (peroxidase, DAB: X100)

mouse
cyclin A Ki-67

Ki-67 cyclin A (parabasal cell) 가
300 cyclin A (Fig. 1a, 1b). CIN
Ki-67 Cyclin A cyclin A Ki-67
Ki-67 (labeling index) 가 Ki-67 cyclin A
Mannk-Whitney U test p < 0.005 (Fig. 2a, 2b, 3a, 3b).

Fig. 1a: The cyclin A expressed in the nuclei of the parabasal cells of the normal squamous epithelium of the uterine cervix (peroxidase, DAB: X100)

Fig. 2a: The cyclin A expressed in the nuclei of CIN II (peroxidase, DAB: X200)

Fig. 2b: The Ki-67 expressed in the nuclei of CIN II diffusely (peroxidase, DAB: X200)

Fig. 1b: The Ki-67 expressed both in the nuclei of the parabasal cells and the stromal cells of the

Ki-67

cyclin A

(Table 1).

CIN

cyclin A (%)

Fig. 3a: The cyclin A expressed in the nuclei of carcinoma in situ involving glands. (peroxidase, DAB: X200)

Fig. 4a: The cyclin A expressed in the nuclei of the tumor cell nests of the periphery invading the stroma. (peroxidase, DAB: X200)

Fig. 3b: The Ki-67 expressed in the nuclei of carcinoma in situ involving glands diffusely (peroxidase, DAB: X200)

Fig. 4b: the Ki-67 expressed in the nuclei of the tumor cells nests diffusely, and the stromal nuclei as well (peroxidase, DAB: X200)

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(Fig. 4a, 4b)

CIN

Cyclin A Ki-67 cyclin

0.8 ± 0.4 CIN 65.5 ± 9.4

86.5 ± 12.3 가

가

Ki-67

가

Ki-67 cyclin A

Table 1. Labeling Index (LI) of Cyclin A and Ki-67 according to the Histologic Type.

	Normal	CIN	Inv. SCC
Cyclin	0.8 ± 0.4a	65.5 ± 9.4*	86.5 ± 12.3*
Ki-67	1.3 ± 0.7	77.8 ± 12.9*	92.2 ± 17.6*

CIN: cervical intraepithelial neoplasia. Inv.SCC: invasive squamous cell carcinoma.

Each number of the labeling index indicates the mean ± the standard deviation.

*Significantly different from that of the normal epithelium(p < 0.005)

Table 2. Labeling Index(LI) of cyclin A and Ki-67 according to the Histologic Subtypes

	Normal	CIN			Inv. SCC			
		CIN I	CIN II	CIN III	Kerat.	LCNonk.	Int.	Small
Cyclin A	0.8 ± 0.4	32.5 ± 5.7	75.8 ± 9.0	83.2 ± 13.4	87.3 ± 11.3	87.0 ± 13.2	89.2 ± 15.2	82.3 ± 9.4
Ki-67	1.3 ± 0.7	51.8 ± 9.8	87.9 ± 11.3	93.6 ± 17.5	94.3 ± 19.3	94.1 ± 21.1	90.4 ± 13.5	89.9 ± 16.3

CIN: cervical intraepithelial neoplasia.

LCNonk.: large cell nonkeratinizing type

SCC: squamous cell carcinoma.

Small: small cell type.

Kerat.: keratinizing type.

가

(eukaryotic cell)

CIN I, II, III 32.5 ± 5.7 , 75.8 ± 9.0 83.2 ± 13.4
가 가

cyclin – dependent

cyclin A

kinases(CDKs)

cyclin

가

Ki-67

CIN

CDKs

DNA

가

CIN I

CIN II

(phosphorylation)

cyclin 30

가 (Table 2).

가

(1) G1
cyclin C, D1, D2, D3 E가 , (2) S

cyclin A, (3) G2/M

cyclin B1, B2

cyclin G p53

가

가

cyclin A

cyclin

B

가

DNA

cyclin

A

가 B

가

cyclin

G1(gap 1) , DNA
DNA가

S(synthesis) ,
G2(gap 2)

A

B

(hybrid protein)

M(mitosis)

4

cyclin dependent kinase(CDK)

S G2/M

DNA

(Go)

G1

가

2. cyclin A

G1

M

가

13 cyclin A G1/S

cdk2

M

cdc2

check

check point

G1/S

G2/M

cyclin A/cdk2

pRB

G1/S

15). cyclin A/cdc2
lamin labeling index
가 77.8 ± 12.9%
cyclin A 가 , 92.2 ± 17.6%
cyclin A 가 CIN 가
4), (leukemic cell line)5) labeling index CIN I, II, III가 51.8 ± 9.8%,
cyclin A 87.9 ± 11.3%, 93.6 ± 17.5% 가
6). 86.5 ±
cyclin A cyclin A 12.3%
가 가
anchorage independent growth, . Cyclin
A cyclin A Ki-67
. Cyclin A 2 check point
cyclin A G2/M 가
cyclin A
가
가 cyclin A
cyclin A
가
가
가
Ki-67
3H-thymidine incorporation S
cyclin A
Ki-67
16).
PCNA(proliferating nuclear antigen)
PCNA
가 17), 18), 19) V.
20) PCNA가
PCNA 가
가
Ki-67
Go G1, S, G2 M cyclin A S G2/M
check point
Ki-67 cyclin A posi-
tive regulator
Ki-67
가 Ki-67 Go

1. Cyclin A Ki-67 30
20
3. cyclin A CIN
I, II, III 32.5 ± 5.7%, 75.8 ± 9.0%,
83.2 ± 13.4% Ki-67 CIN
CIN I, II, III 51.8 ± 9.8%,
87.9 ± 11.3%, 93.6 ± 17.5%
4. cyclin
A Ki-67
cyclin A Ki-67
2. Cyclin A
0.8 ± 0.4%,
65.5 ± 9.4% and 86.5 ± 12.3%
Ki-67

- Reference -

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