Article is available online at http://www.webio.hu/por/2005/11/1/0032

ARTICLE

Immunohistochemical Analysis of c-Myc, c-Jun and Estrogen Receptor in Normal, Hyperplastic and Neoplastic Endometrium

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To evaluate the role of c-jun and c-myc proto-oncogenes in normal, hyperplastic and neoplastic endometrium in relation to estrogen receptor (ER) status and to investigate whether these genes can be related to other histopathological features of endometrial carcinoma, 32 endometrial carcinomas, 38 endometrial hyperplasias and 22 cyclic endometria (10 proliferative and 12 secretory) were evaluated histologically. Endometrial hyperplasia cases were classified as simple and complex hyperplasia without atypia, and atypical hyperplasia. Endometrial carcinoma cases were subtyped according to the International Society of Gynecological Pathologists. Modified FIGO system was used for both grading and staging. Immunohistochemical examination was performed using antibodies to ER-alpha, c-myc and c-jun with streptavidin-biotin-peroxidase technique. The mean percentage of ER-alpha positive cells changed cyclically during the menstrual cycle, and it was the highest (96%) and the lowest (31.6%) in proliferative and carcinomatous endometrium, respectively. There was a statistically significant difference between proliferative and secretory phases and proliferative and carcinomatous endometrium in relation to ER-alpha staining ($p<0.05$). There was also a statistically significant difference with respect to ER-alpha reactivity between secretory phase and each hyperplastic group, as well as between the carcinoma group and each hyperplastic group ($p<0.05$). Although not significant, the mean percentage of c-myc expressing cells in the carcinoma group was higher (15.3%) than that of proliferative phase and hyperplastic groups. The mean percentage of c-jun positive cells in proliferative endometrium was slightly higher than in secretory endometrium, and it was the highest in atypical hyperplastic endometrium (28.3%), but there was no statistically significant difference between the groups. In carcinoma cases, a positive correlation was observed between c-jun positivity and tumor grade ($p=0.027$, $r=0.3908$), but such a correlation with c-myc was not found. A positive correlation was detected between ER-alpha and c-myc expression ($p=0.038$, $r=0.3686$). A progressive loss of ER seems to be correlated with increasing malignant transformation. C-myc expression might play a role in the development of endometrial carcinoma via ER. The association between c-jun and ER appears to be lost in endometrial carcinoma. The relationship between c-myc, c-jun and ER appears to be altered in endometrial carcinoma compared to that of menstrual endometrium. (Pathology Oncology Research Vol 11, No 1, 32–39)

Key words: human endometrium, estrogen receptor, c-myc, c-jun

Introduction

Endometrium is a dynamic environment in which growth and proliferation is regulated by hormones.[1] The proliferation of normal endometrial glandular cells and endometrial carcinoma cells expressing estrogen receptor (ER) are increased by estrogen. Estrogen-induced growth mechanism of the normal and malignant endometrium is important for the prevention of endometrial neoplasia under unopposed estrogen environment.[1,2] The mechanism of estrogen stimulation in the uterus is regulated by a series of gene expressions, which is still not completely understood.[1,3] ER mediates hormonal action, and hormone-occupied ER modulates the transcription of target genes by binding to their estrogen-responsive element (ERE).[4] Binding of activated ER complexes to nuclear acceptor sites is followed by an alteration in the transcription of specific

Received: Oct 20, 2004; *accepted:* Dec 25, 2004
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genes.[5] Several studies have demonstrated that estrogen treatment induces immediate and transient activation of a number of nuclear proto-oncogenes in the uterus, including c-myc, N-myc, c-fos, c-jun, jun-B, jun-D.[2,4,6,7] Increased expression of these nuclear proto-oncogenes appears to be a direct effect of estrogen.[4] Furthermore, down-regulation of nuclear proto-oncogenes such as c-myc, c-jun, c-fos by progesterone has also been reported.[5] Among such estrogen-inducible proteins, some are considered to contribute to malignant transformation in the endometrium.[8]

C-myc and c-jun are two distinct nuclear proto-oncogenes known as immediate early genes. They encode transcriptional regulatory proteins, which may be required for cell growth and differentiation. It is hypothesized that these genes are not only involved in normal growth, but may also play a role in the development of neoplasia.[8,9] C-jun activation is related to proliferation, differentiation, and apoptosis,[3,10] and is required for progression through the G1 phase of the cell cycle. It is activated by a variety of extracellular stimuli including growth factors, cytokines, cellular stress and UV radiation, and regulates cell cycle progression and apoptosis by distinct mechanisms.[11] C-jun encodes a DNA-binding protein associated with the transcription factor AP-1 complex.[5,11,12] This complex binds to the AP-1 DNA element to regulate the transcription of genes containing this element.[5] This protein product, AP-1, is involved in the estrogen-signaling pathway and affects short- and long-term responses to several extracellular stimuli by inducing transcription of target genes.[3,11] C-myc gene, a cellular homologue of viral v-myc oncogene, encodes a nuclear chromatin-associated protein.[13,14] C-myc is a highly conserved protein, which suggests that it may serve a critical function. A rapid and transient increase in the expression of c-myc gene has been observed in many quiescent cells after mitogenic stimulation.[14] The expression rate of c-myc increases by 10-20 fold when the cells are stimulated by different growth factors, whereas resting cells show lower levels of c-myc expression.[15]

C-jun and c-myc genes may be important regulators of estrogen-induced growth and differentiation. Many studies have demonstrated that c-jun expression changes cyclically between phases of the menstrual cycle.[8,10,16] However, different results have been reported in studies investigating the role of c-jun gene in endometrial carcinomas.[1,2,8,17] Estrogen induces rapid transient c-myc gene expression with cell type-specific localization.[13,14,18] Studies on human uterus have shown that the level of c-myc is significantly higher in endometrium than in other uterine corpus tissues.[16] These studies may explain the existence of a complex regulated mechanism between nuclear proto-oncogenes and estrogen. The mechanism of progression from hyperplasia to endometrial adenocarcinoma, the role of these proto-oncogenes in the development of endometrial carcinoma, and the association with ER have not been fully elucidated. Thus, to understand the hormonal regulation of c-myc and c-jun in the endometrium, we examined c-myc, c-jun, and ER-alpha expression immunohistochemically in different types of endometrial tissues involving cyclic endometrium, hyperplasia and carcinoma. We also evaluated if the expression of these genes can be related to histopathological features of endometrial carcinoma.

Materials and methods

Histopathology

In this study, we examined a total of 92 cases including 32 cases of endometrial carcinoma and 38 cases of endometrial hyperplasia together with 10 proliferative and 12 secretory endometria obtained from archival materials. Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy and curettage material were included in the study. Sections of 5 μm thickness were cut from 10% formalin-fixed, paraffin-embedded material and stained with hematoxylin and eosin. The cases of endometrial hyperplasia were classified as simple and complex hyperplasia without atypia and atypical hyperplasia, proposed by International Society of Gynecological Pathologists (ISGYP).[19] Endometrial carcinoma cases were classified according to ISGYP.[20] Modified FIGO[21] system was used in both grading and staging of endometrial carcinoma cases. Clinical information was obtained from the hospital files.

Immunohistochemistry

Immunohistochemistry was performed using streptavidin-biotin-peroxidase technique (Histostain-plus bulk kit, 85-9043, Zymed, USA), and monoclonal antibodies to c-myc (NCL-cMYC-9E11, Novocastra, UK, 1:100), c-jun (NCL-cJUN-DK4, Novocastra, 1:40), and ER-alpha (NCL-ER-6F11, Novocastra, 1:30) were used in the study. The sections were incubated with AEC for 5 min. Finally the sections were counterstained with Mayer's hematoxylin and mounted with aqueous mounting medium. The primary antibodies were omitted in negative controls. C-myc positive lung and breast carcinoma sections, ER and c-jun positive breast carcinoma cases were used as positive controls. Epithelial component was assessed in all cases. The extent of staining was determined semiquantitatively as the percentage of positively stained cells of the entire slide.

Statistical analysis

Data were analyzed by Student's t-test, one-way variant analysis (Anova) and Kruskal-Wallis variant analysis. Spearman's rank correlation coefficient was used to evaluate the correlation between immunoreactivity of carcinomas and histopathological variables. A p value less than 0.05 was considered as significant.

Table 1. **Clinicopathological features of endometrial carcinomas**

Patient No.	*Age*	*Tumor type*	*Grade*	*Myometrial invasion*	*Pathological stage*	*ER-α (%)*	*C-jun (%)*	*C-myc (%)*
1	54	Endometrioid	3	>1/2	IVB	50	40	10
2	59	Endometrioid	1	<1/2	IB	5	0	0
3	60	Endometrioid	1	>1/2	IIIA	0	5	5
4	64	Endometrioid	3	>1/2	IC	10	0	0
5	67	Endometrioid	1	<1/2	IIIC	0	10	10
6	57	Endometrioid	1	<1/2	IB	40	0	20
7	72	Endometrioid	1	>1/2	IIA	50	0	10
8	54	Endometrioid	1	No	IA	30	0	0
9	36	Endometrioid	1	PC*		5	0	0
10	61	Endometrioid	3	>1/2	IVB	60	0	5
11	76	Endometrioid	2	>1/2	IC	30	30	0
12	38	End. sq. diff.†	1	No	IA	70	0	0
13	62	Endometrioid	1	<1/2	IB	10	0	50
14	72	End. sq. diff.†	2	No	IA	80	80	20
15	50	Endometrioid	2	<1/2	IIIC	60	20	70
16	52	Endometrioid	1	No	IA	40	0	30
17	55	Endometrioid	3	>1/2	IVB	0	0	5
18	65	Endometrioid	2	<1/2	IIA	50	0	10
19	74	Endometrioid	2	<1/2	IIB	70	0	40
20	78	Endometrioid	2	>1/2	IIB	50	70	50
21	56	End. sq. diff.†	1	<1/2	IB	50	0	5
22	67	Endometrioid	1	>1/2	IC	80	50	5
23	66	Endometrioid	2	<1/2	IB	0	0	0
24	68	End. sq. diff.†	2	<1/2	IB	40	0	5
25	55	End. sq. diff.†	3	>1/2	IIIA	20	0	0
26	60	Endometrioid	2	No	IA	10	0	20
27	49	Endometrioid	1	No	IA	20	0	0
28	71	Endometrioid	1	<1/2	IB	40	5	30
29	78	Endometrioid	2	<1/2	IB	10	20	0
30	80	Serous papillary	3	PC*		5	40	0
31	65	Serous papillary	3	<1/2	IB	20	50	20
32	69	Clear cell	3	No	IA	5	50	70

†Endometrioid carcinoma with squamous differentiation *Diagnostic curettage

Results

The cases of endometrial hyperplasia were classified as 13 simple and 13 complex hyperplasias without atypia, and 12 atypical hyperplasias. Patients' age ranged from 23 to 58 years (median: 44 years). The carcinomas were subtyped as 29 endometrioid, 2 serous papillary carcinomas, and 1 clear cell carcinoma. The ages of carcinoma patients ranged from 36 to 80 years (median: 62 years). There was a statistically significant difference in age between the hyperplasia and carcinoma cases ($p=0.0001$). There was no significant difference among hyperplastic groups in relation to age ($p>0.05$). *Table 1* summarizes the clinicopathological features of the endometrial carcinomas.

Immunohistochemistry

ER-alpha expression was demonstrated in the nuclei of epithelial cells in normal, hyperplastic and carcinomatous endometrium. *Table 2* shows the percentages of ER-alpha expressing cells in all groups. The mean percentage of ER-alpha positive cells was the highest (96%) in the proliferative endometrium, whereas it was the lowest (31.6%) in the carcinoma group. There was a statistically significant difference between proliferative and secretory endometrium, and proliferative and carcinomatous endometrium in relation to ER-alpha staining ($p<0.05$). There was also a statistically significant difference with respect to ER-alpha reactivity between secretory endometrium and each hyperplastic group, as well as between the carcinoma group and

Table 2. **Comparison of the percentages of ER-alpha positive cells between groups**

Groups	*N*	*ER-α positive cells (%)*				
		Min	*Max*	*Mean*	*SD*	
Proliferative phase	10	80	100	96	7	p<0.05 vs. cancer, secretory
Secretory phase	12	10	80	42.1	24.6	
Simple hyperplasia	13	60	100	82.3	14.2	p<0.05 vs. cancer, secretory
Complex hyperplasia	13	50	90	72.3	14.2	p<0.05 vs. cancer, secretory
Atypical hyperplasia	12	30	100	84.2	21.5	p<0.05 vs. cancer, secretory
Cancer	32	0	80	31.6	25.6	

each hyperplastic group (p<0.05). There was no statistically significant difference in relation to the percentage of ER-alpha staining among hyperplastic groups (p>0.05). A correlation was not found between ER-alpha immunostaining and clinicopathological features of endometrial carcinomas.

Cytoplasmic finely granular or perinuclear granular c-myc expression was found in all groups *(Figure 1a,b)*. The percentages of c-myc expression in all groups were summarized in *Table 3*. The mean percentage of c-myc reactivity was highest in the secretory endometrium (20%) compared to that of the other groups, but there was no statistically significant difference between the groups (p>0.05). Although not significant, the mean percentage of c-myc expressing cells in the carcinoma group was higher (15.3%) than that of the hyperplastic and proliferative endometrial groups (p>0.05). In the endometrial carcinoma cases, no correlation was detected between the histopathological features and c-myc expression, whereas there was a significant positive correlation between ER-alpha positivity and c-myc expression (p=0.038, r=0.3686).

Nuclear expression of c-jun was detected in all groups *(Figure 2a,b)*. *Table 4* shows the percentages of cells with c-jun staining in all groups. The mean percentage of c-jun reactivity was the highest in the atypical hyperplastic endometrium (28.3%), while the lowest expression was detected in complex hyperplasia (1.2%). The mean percentage of c-jun positive cells in proliferative endometrium (14.5%) was slightly higher than that in secretory endometrium (11.7%). There was no statistically significant difference between the groups (p>0.05). A positive correlation was observed between the histological grade and c-jun positivity in the endometrial carcinoma cases (p=0.027, r=0.3908), but no correlation was obtained between ER-alpha and c-jun expression. In non-endometrioid carcinomas, the mean percentage of c-jun appeared to be higher than in endometrioid ones (*Table 1*).

Discussion

Estrogen is the most important factor in the development and differentiation of normal endometrium and endometrial carcinoma.[8,22] It is well known that ER levels are higher in the proliferative phase than those in the secretory phase of the cycle.[23-28] Mean ER values appear to be higher in hyperplastic compared to carcinomatous endometrium, and several studies have shown that ER expression decreases as the lesions proceed to endometrial carcinoma.[23-29] Huang et al[24] found that ER immunoreactivity was more variable among atypical hyperplasia cases, with a trend towards decreased ER rates compared to non-atypical types. However, Punnonen et al[30] reported that ER lev-

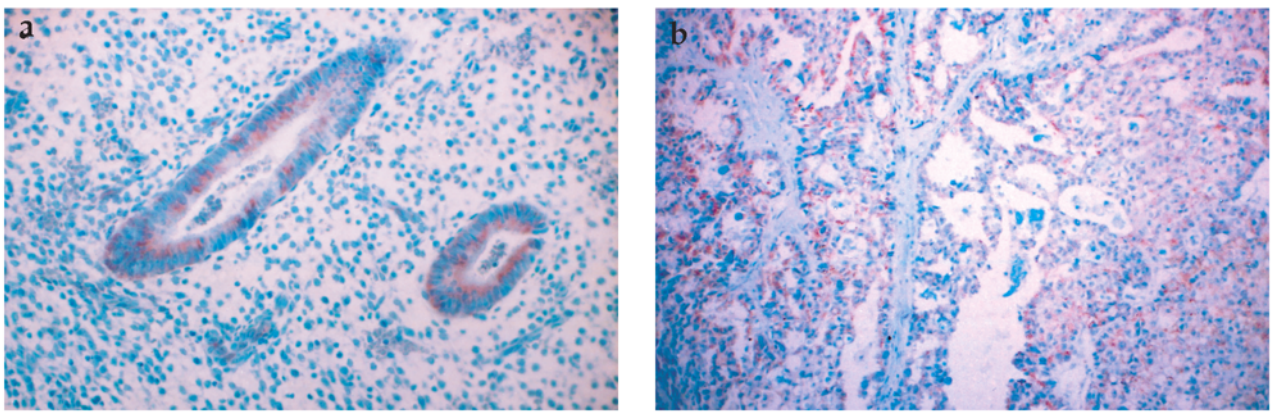

Figure 1. *Perinuclear cytoplasmic granular c-myc expression in proliferative endometrium (AEC; x200)* ***(a)*** *and endometrial carcinoma (AEC; x100)* ***(b)***.

Table 3. **Comparison of the percentages of c-myc positive cells between groups**

Groups	N	c-myc positive cells (%)			
		Min	Max	Mean	SD
Proliferative phase	10	0	50	11	16.6
Secretory phase	12	0	60	20	17.5
Simple hyperplasia	13	0	40	8.1	12
Complex hyperplasia	13	0	40	10.4	13.3
Atypical hyperplasia	12	0	50	10	16.7
Cancer	32	0	70	15.3	20.4

els were extremely high especially in atypical hyperplasia cases when compared to those without atypia and to the carcinoma cases. In the current study, we found that the percentage of ER-alpha positive cells decreased gradually from proliferative endometrium through hyperplasia to carcinoma. ER status changed cyclically in normal endometrium. Although not statistically significant, it tended to be lower in the hyperplastic compared to the proliferative endometrium. There was no statistically significant difference among hyperplastic groups. However, their ER values were significantly higher than that of carcinomatous endometrium. Many studies have shown that endometrial carcinomas had significantly lower ER levels than hyperplastic and proliferative endometrium.[23,25,29] Type 1 endometrial adenocarcinoma, in contrast to type 2, is generally accepted to be an endocrine-related neoplasm, and like normal endometrium, many of them contain ER-alpha.[26] Several studies have demonstrated that ER content in endometrial carcinomas correlates with clinicopathological parameters, prognosis and survival.[26,31-33] ER level also depends on tumor grade and decreases with higher histologic grades.[23-25,27,28,30] In our study, we detected that ER-alpha expression was the lowest in the carcinoma group. Although no association between ER-alpha and histopathological parameters was found, in three non-endometrioid carcinomas ER rate tended to be lower than that of endometrioid ones.

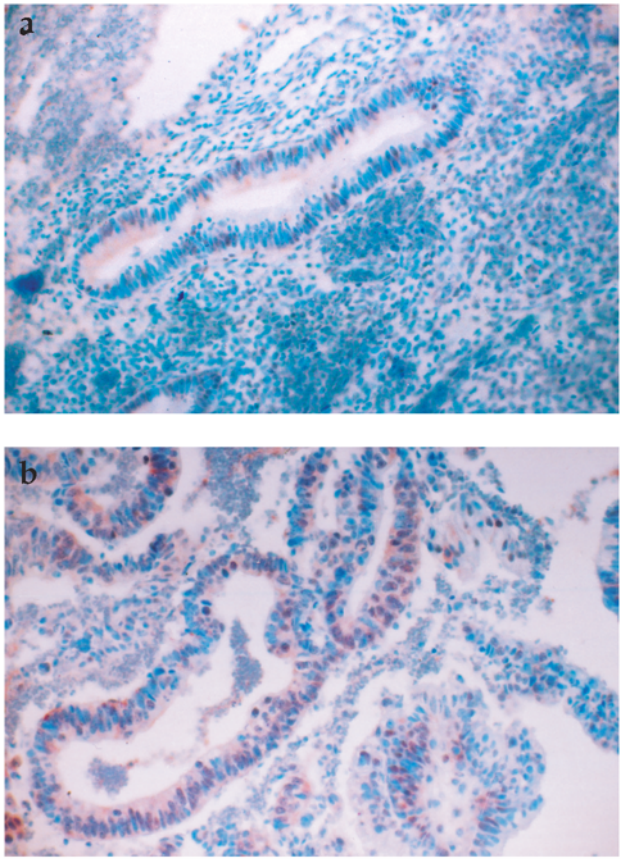

Figure 2. *Nuclear c-jun expression in the proliferative endometrium (AEC; x200)* ***(a)*** *and atypical hyperplasia (AEC; x400)* ***(b)***

C-jun gene may be an important regulator of estrogen-induced growth and differentiation, and an upregulation of its expression has been shown in response to estrogen in many studies.[2,4,6,7] However, a few studies reported a decrease in its expression in rat uterine epithelium.[34,35] It is suggested that estradiol-induced proliferation of normal endometrial glandular cells is initiated by transcriptional activation of cyclin D1 via binding of c-jun to AP-1 sequence, in contrast to that of endometrial carcinoma cells.[2] In human uterine tissues, it was demonstrated that c-jun mRNA expression levels changed cyclically in endometrium between the phases of the menstrual cycle, and increased significantly after estrogen administration.[8,10,16] However, Salmi et al[10] and Nephew et al[1] reported that there was nuclear c-jun immunostaining in the human endometrium throughout the menstrual cycle, which was not cyclic. On the other hand, Udou et al[3] showed cyclic changes of c-jun protein in epithelial cells of endometrium immunohistochemically, which was highest during proliferative and lowest during late secretory phase. In our study, the mean percentage of c-jun expressing cells was slightly decreased in secretory phase compared to proliferative endometrium. This situation could be due to a positive correlation between c-jun and estrogen,

Table 4. **Comparison of the percentages of c-jun positive cells between groups**

Groups	N	c-jun positive cells (%)			
		Min	Max	Mean	SD
Proliferative phase	10	0	50	14.5	19.2
Secretory phase	12	0	70	11.7	22
Simple hyperplasia	13	0	50	12.3	16.9
Complex hyperplasia	13	0	10	1.2	3
Atypical hyperplasia	12	0	80	28.3	29.8
Cancer	32	0	80	14.7	23.4

and estrogen action may be mediated by c-jun gene in normal endometrium. Thus, c-jun proto-oncogene may be an important mediator of estrogen action in human endometrial cell proliferation.

Different results have been reported in the studies investigating the role of c-jun gene in endometrial carcinomas. Fujimoto et al[8] revealed that c-jun mRNA expression was higher in endometrial carcinoma than in its normal counterpart, and was also higher in grade 1 endometrial cancers when compared to grade 2 or 3 carcinomas. Yokoyama et al,[36] on the other hand, reported that patients with c-jun positive tumors had significantly worse prognosis than those with c-jun negative ones, and c-jun expression was also found to be associated with the presence of lymph node metastasis independently. Therefore, they suggested that c-jun might reflect the metastatic potential of endometrial carcinomas. However, Nephew et al[1] did not find a statistical correlation between c-jun expression and clinicopathological features, although they observed that c-jun expression tended to be higher in grade 3 tumors. On the other hand, Salmi et al[17] did not show any correlation between either c-jun and ER expression, or c-jun expression and histological grades. They suggested that there might be loss of association between c-jun expression and ER in malignant endometrium in contrast to normal cyclic endometrium. In our study, we found a positive correlation between c-jun immunostaining and tumor grade in endometrial carcinomas, but such a relation was not detected between c-jun and ER-alpha. These results may suggest that an association between ER and c-jun may be different in normal cyclic endometrium from that in malignant endometrium. During progression from hyperplasia to carcinoma, changes in the percentage of c-jun expressing cells were observed. While the mean percentage of c-jun immunoreactivity was the lowest in complex hyperplasia, it was the highest in atypical hyperplasia. To our knowledge, these findings regarding c-jun immunoreactivity are the first reported findings showing a sequence from hyperplasia to neoplasia. According to these results, positive correlation previously reported between c-jun and estrogen in cyclic endometrium may alter during hyperplasia-carcinoma sequence. The association between ER and c-jun and hormone-mediated signal pathways in malignant endometrium seems to be different from that of normal endometrium.

Animal studies have shown that estrogen induces rapid transient c-myc gene expression with cell type-specific localization.[13,14,18] After estrogen injection a rapid accumulation of c-myc protein was detected in the nuclei of endometrial epithelial cells immunohistochemically. Similarly, studies on human uterus have shown that there was a tissue difference in c-myc expression related to estrogen action, and the level of c-myc was significantly higher in endometrium than in other uterine corpus tissues, while the level of c-myc did not change either during menstrual cycle or following estrogen treatment.[16] However, Odom et al[37] reported that there was a cyclic variation in the expression of c-myc protein product, and it was higher in the proliferative than in the secretory phase. In this study, the product identified by the anti-myc monoclonal antibody was detected in both the nucleus and the cytoplasm. A nuclear distribution was observed in actively dividing cells in the proliferative phase, while in differentiated cells of the secretory phase the immunostaining was primarily cytoplasmic. Similarly, Jack et al[38] noticed that nuclear c-myc reactivity was present in actively dividing cells and in some tumors. However, its localization was perinuclear and cytoplasmic in most normal cells. Schenken et al[39] and Bai et al[40] have reported similar findings. In our study, we obtained perinuclear staining of c-myc except in the secretory phase in which diffuse cytoplasmic staining was found. Nuclear staining was not observed. These findings suggest that the localization of c-myc protein in vivo might differ in cells that are dividing as opposed to those that are arrested or terminally differentiated, and the nuclear and cytoplasmic c-myc protein may have different functions. On the other hand, Loke et al[41] showed nuclear c-myc staining in frozen sections of various normal adult mouse tissues, particularly in highly proliferative cells; however, when these tissues were studied after formalin fixation, a loss of nuclear staining and cytoplasmic immunoreactivity were observed.

There are few reports about c-myc gene expression in premalignant and malignant lesions of the endometrium. Bai et al[40] found that the overexpression and localization of the c-myc product may have an important role in the initiation, differentiation and progression of endometrial carcinoma. They demonstrated increased expression of c-myc product in endometrial hyperplasia and carcinoma compared to normal endometrium, and also showed that different staining patterns of c-myc might correlate with the degree of differentiation of carcinoma. In our study, the mean percentages of c-myc positive cells in all hyperplasia groups were similar to those in the proliferative phase, but in endometrial carcinoma cases c-myc levels appeared to increase compared to the other groups. While no correlation was found between c-myc expression and histopathological features in endometrial carcinomas, we found a positive correlation between ER-alpha and c-myc expression. This finding may suggest that estrogen may induce c-myc expression leading to neoplastic transformation in human endometrium. While some studies reported no significant relationship between c-myc expression and histopathological factors or clinical outcome,[36,42,43] other studies showed that c-myc expression was associated with higher grade, advanced stage and poor differentiation of endometrial carcinomas.[44,45] Ambros[46] detected cytoplasmic c-myc immunoreactivity

in the tumor cells. Since intense staining was frequently seen in tumors with deep myometrial and vascular invasion, and low-grade tumors with superficial invasion showed faint to moderate staining, it was suggested that high c-myc expression could be associated with tumor cells capable of myometrial and vascular invasion. Furthermore, it was reported that nuclear and cytoplasmic c-myc stainings were important factors in predicting survival in endometrial carcinomas.[47] On the other hand, Sasano et al[48] demonstrated c-myc amplification in primary and metastatic serous papillary adenocarcinomas of endometrium in contrast to endometrial hyperplasia and adenocarcinoma cases.

In summary, ER level is regulated cyclically in normal endometrium, and it is slightly decreased in endometrial hyperplasia compared to proliferative phase. A progressive loss of ER seems to be correlated with increasing malignant transformation, and the greatest differences in ER level were found between proliferative and malignant endometrium, and hyperplastic and malignant endometrium. C-jun and c-myc expression in normal cyclic endometrium appear to be altered according to phases. During progression from hyperplasia to carcinoma c-myc expression may play a role in the development of endometrial carcinoma, in which estrogen may induce c-myc expression leading to neoplastic transformation in human endometrium. C-jun expression seems to be correlated with tumor grade, and the association between ER and c-jun previously reported in menstrual endometrium appears to be lost in endometrial carcinoma. The relationship between c-myc, c-jun and ER appears to be altered in endometrial hyperplasia-carcinoma sequence compared to menstrual endometrium.

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