行政院國家科學委員會補助專題研究計畫成果報告

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※子宮之甲型和乙型動情素接受體於信息核醣核酸的表現※

※Expression of Estrogen Receptor Alpha and Beta Subtypes ※

※in Normal and Neoplasia Tissues of Uterus ※

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本成果報告包括以下應繳交之附件：

□赴國外出差或研習心得報告一份

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□出席國際學術會議心得報告及發表之論文各一份

□國際合作研究計畫國外研究報告書一份

執行單位：中山醫學院，附設醫院

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題目與主持人資料

計畫類別(單選)	☑一般型計畫 ☐特約研究計畫 ☐新進人員補助計畫 ☐其它 _____				
研究型別	個別型計畫				
計畫歸屬	☐自然處☐工程處☑生物處☐人文處☐科教處☐永續會☐應用科技小組				
本計畫名稱	中文	子宮之甲型和乙型動情素接受體於信息核醣核酸的表現			
	英文	Expression of Estrogen Receptor Alpha and Beta Subtypes in Normal and Neoplasia Tissues of Uterus			
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本次申請主持國科會各類研究計畫共 1 件。 本件在本次所申請之計畫中優先順序(不得重複)為第 1 (共同主持之計畫不予計入)					
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三、主要研究人力

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主持人	林隆堯	12	主持計畫，資料的統計與分析及實驗結果的寫作
協同主持人	林嬪嬪	12	RT-PCR 操作之品質管制，動情素信息核醣核酸表現之判讀解釋
共同主持人	林培正	12	RT-PCR 操作之品質管制，動情素信息核醣核酸表現之評估
共同主持人	陳進典	12	1. 實驗規劃 2. 於手術中由病人身上取得檢體 3.評估疾病的臨床症候及檢體選取分類 4.檢查結果與臨床資料之整合分析及實驗成果的寫作
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主持人、共同主持人、協同研究人員近三年內曾參與之專題研究計畫。

姓名	計畫名稱 （本會補助者請註明編號）	計畫內擔任工作	起迄年月	補助機構
林隆堯	The prevalence of pre-menstrual syndrome and the treatment effect of pyridoxine in Taiwanese adolescence	主持人	83/01-85/01	哈佛大學
林隆堯	台中地區未婚婦女流產流行病學研究	主持人	79/07-80/07	婦幼中心
林隆堯	PCK 之假孕蛻膜形成之活性變化	主持人	85/07-86/06	中山醫學院
林嬪嬪	雌性激素對 benzo[a]pyrene 在腺性肺癌細胞株活化環狀芳香氫感受器之影響探討 (NSC 86-2314-B-04-067)	規畫，主持計畫	86/02-86/07	國科會

林嬪嬪	台灣地區肺癌發生之毒理機轉的探討-子計畫五 CYP1A1 與 GST1 遺傳多形性之探討	規畫，主持計畫	85/07-88/06	國家衛生研究院
林嬪嬪	建立大鼠擬表皮模式以評估皮膚毒性與毒物經皮膚吸收代謝之能力(NSC 87-2314-B-040-025)	規畫，主持計畫	86/08-87/07	國科會
林嬪嬪	探討食用油煙霧於人類肺細胞株之毒性與誘導基因表現之訊息傳導途徑 (NSC 88-2314-B-040-007)	規畫，主持計畫	87/08-88/07	國科會
林培正	Analysis of Pax6 expression during vertebrate head development	博士班研究生	82/01-86/01	愛丁堡大學
林培正	Establishment of an in vitro mouse embryo implantation model (CSMC 87-OM-B-008)	主持人	87/10-88/9	中山醫學院
林培正	The effect of ROS scavengers on sperm motility and acrosome reaction (CSMC 87-OM-B-009)	共同主持人	87/10-88/9	中山醫學院

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專任助理	最高學歷	中國醫藥學院　學校 營養　系(所)			中國醫藥學院　學校 營養　系(所)		
	修業期間	83　年　9　月至　87　年　6　月			83　年　9　月至　87　年　6　月		
兼任助理	講師/助教	任職起始日期：　年　月			任職起始日期：　年　月		
	研究生/大專學生	入學日期：　87　年　9　月 就讀學校系所：中山醫學院毒理所			入學日期：　87　年　9　月 就讀學校系所：中山醫學院毒理所		

中文摘要

本研究主要比較子宮頸甲、乙型動情素接受體於不同月經週期、停經期前後、正常和癌組織之訊息核糖核酸之表現。

結果發現，子宮頸甲、乙型動情素接受體之訊息核糖核酸表現，於增殖、分泌期沒有差異。然而，即使乙型動情素接受體於停經期前後表現沒有差異；但是，甲型動情素接受體停經後卻呈有意義之消失。雖然，在跟正常組織比較下，甲、乙型動情素於癌組織之表現，都分別有一、二例呈現消失情形，但並未達到統計上的意義。

本研究所得結論是，只有甲型動情素接受體牽涉到正常停經後子宮頸的變化，至於癌組織的變化可能都和兩種動情素接受體沒有關聯。

Abstract

Objective: To detect changes in transcript expression for estrogen receptors alpha and beta in the uterine cervix, comparing premenopausal and postmenopausal status, different menstrual phases and carcinomatous tissues.

Methods: Nineteen normal portions of cervical samples were obtained, one from each of twelve cases of uterine myoma and from each of seven cervical cancer; and seven carcinomatous samples, one from each of the seven cervical cancer. Reverse transcription polymerase chain reaction was used to detect the transcript expression of estrogen receptors alpha and beta in all samples. Nineteen normal samples were divided according to premenopausal and postmenopausal status and compared for estrogen receptor subtype mRNA expression. Thirteen normal premenopausal cervical samples were divided according to proliferative and secretory phases for comparison. In addition, mRNA expression of estrogen receptors alpha and beta for the seven carcinomatous samples was compared with those of their normal counterparts. Fisher's exact test was used for statistical analysis.

Results: Comparing premenopausal and postmenopausal normal cervical samples, a statistically significant difference was demonstrated for the estrogen receptor alpha mRNA expression ($P < 0.05$), but not for the receptor beta. For the normal premenopausal cervical samples, the transcript expression for each estrogen receptor subtype was not affected by menstrual phases. Further, no significant difference was revealed for transcript expression of estrogen receptors alpha and beta ($P > 0.05$) comparing carcinomatous and normal portions from the cervical cancer samples.

Conclusion: Only the absence of the estrogen receptor alpha in the cervical tissues correlates with postmenopausal status. Differential transcript expression for estrogen receptor subtypes is confirmed in the postmenopausal cervix, but is not implicated for cervical carcinogenesis.

Objective and Background

Our previous study used reverse transcription polymerase chain reaction (RT-PCR) to demonstrate that all tissue samples from pre- and postmenopausal vaginal walls contained transcripts for the estrogen receptor alpha (ER α); estrogen receptor beta (ER β) mRNA, however, being detected in all of the premenopausal but none of the postmenopausal vaginal wall samples.[1] Sicne human ER β was introduced in 1996[2], there has been no study using RT-PCR to investigate mRNA expression of ER β in the uterine cervix for postmenopausal or premenopausal status (including proliferative or secretory phases) leaving unresolved the question of different mRNA expression for each ER subtype.

Although several larger studies have shown that the estrogen receptor content for carcinomas of the uterine cervix has no prognostic value, ER β, however, was not included in these envestigations.[3,4] If the significance of ER subtypes in cervical cancer is to be evaluated, the distribution of these subtypes should be correlated with the occurrence of this disease. Brandenberger et al have demonstrated that, in a comparison of ovarian cancer samples, the level of ER α mRNA was similar or slightly greater than that corresponding to samples from normal ovaries, whilst the level of ER β mRNA levels was reduced.[5] To date, there have been no studies

investigating the expression of ER β and cervical cancer, leaving the question of the role of different ER subtypes in cervical carcinogenesis unexplored.

The aim of this study was to detect changes in mRNA expression, for each ER subtype, in the cervix of normal human variants according to menstrual status (pre- and postmenopause and during proliferative, and secretory phases) and pathological (carcinomatous) status.

Materials and Methods

Normal portions of cervical samples were obtained from twelve patients (patient numbers 1-12) with uterine myoma, who underwent total abdominal hysterectomy and seven patients (patient items A-G) with cervical cancer, who underwent radical abdominal hysterectomy and bilateral pelvic lymphadenectomy between May 1996 and May 1997. These patients were divided into pre- and postmenopausal groups. Ages and parities of the thirteen premenopausal women ranged from 39 to 51 years (43.2 $\pm$ 3.4) and nulliparity to five children (median = four), respectively. Ages and parities of the six postmenopausal women ranged from 52 to 65 years (55.2 $\pm$ 7.3) and three to six children (median = five), respectively. The premenopausal group was further divided into proliferative and secretory groups. Ages and parities of the five women in the proliferative group ranged from 39 to 46 years (43.2 $\pm$ 2.8) and nulliparity to four children (median = three), respectively. Ages and parities of the eight women from the secretory group ranged from 39 to 51 years (43.1 $\pm$ 3.9) and one to five children (median = three), respectively. Samples of carcinomatous tissue were obtained from the seven patients with cervical cancer. Patients were staged from Ib to IIb according to International Federation of Gynecology and Obstetrics staging for carcinoma of the *cervix uteri* revised in 1995. Ages and parities of these patients ranged from 40 to 58 years (44.6 $\pm$ 6.3) and one to six children (median = four), respectively. None of the patients included in this study exhibited a history of exogenous hormone use during the six months prior to their lesion was removed. The Chung Shan Institutional Review Board approved the study protocol and informed consent was obtained from all patients. Patient details are displayed in Table 1.

Dissected tissues were snap-frozen and individually stored in liquid nitrogen. Some normal and carcinomatous portions of cervical samples were paraffin-embedded and their pathology confirmed prior to RT-PCR being conducted. Our methodology for RT-PCR was established in a previous publication.[1]

We used Fisher's exact test to compare the mRNA expression for each ER subtype transcript for pre- and postmenopausal cervical samples; and for proliferative and secretory cervical samples. Fisher's exact test was also used for the statistical analysis of mRNA expression for each ER subtype transcript comparing carcinomatous and normal sites for.cervical cancer samples.

Results

An absence of ER α mRNA was noted for most postmenopausal cervical samples (4/6) but rarely for premenopausal cervical samples (1/13), revealing a significant difference for the mRNA expression of ER α comparing pre- and postmenopausal samples ($P < 0.05$). The absence of ER β mRNA, however, was noted for some premenopausal (3/13) and postmenopausal (4/6)cervical samples with no significant difference being demonstrated ($P > 0.05$, Table 1).

There was no significant difference for the mRNA expression of ER α in the comparison of cervical samples during proliferative (4/5) and secretory phases (8/8), as taken from premenopausal subjects ($P > 0.05$). Further, no significant difference was noted for ER β mRNA expression between proliferative (4/5) and secretory phases (6/8) ($P > 0.05$, Table 1).

The ER α and ER β transcripts are expressed consistently in all normal sites from cervical cancer samples (7/7 and 7/7 respectively). For carcinomatous sites, the ER α and ER β mRNA is expressed in most samples (6/7 and 5/7 respectively), but the difference for the mRNA expression of each ER subtype, comparing carcinomatous and normal sites, is not statistically significant ($P > 0.05$, Table 2).

Discussion

Our results demonstrate that, in normal samples from uterine cervix, an absence of ER α mRNA is rarely detected in premenopausal cervical samples but is detected in most postmenopausal cervical samples. There is a significant difference for the ER α mRNA expression between pre- and postmenopausal cervical samples ($P < 0.05$, Table 1). An absence of ER β mRNA, however, is noted in some pre- and postmenopausal subjects, but the absence is not statistically significant (Table 1). Further, in a comparison of normal premenopausal cervical samples in proliferative and secretory phases, the transcript expression of each ER subtype does not differ significantly (Table 1). In pathological cervical samples (cervical cancer), the transcripts expression for both ER α and ER β at carcinomatous sites does not differ significantly from the expression for their normal counterparts (Table 2).

In this study, an absence of ER α transcript expression is detected in most postmenopausal uterine cervical samples, a result compatible with the findings of Press et al, which demonstrated that staining of the estrogen receptor was less intense in the postmenopausal cervix than in the premenopausal cervix.[6] The expression of ER β, however, was not explored in this study. Based on our results, we further demonstrated that an absence of ER α but not ER β is associated with the cervical changes for postmenopausal women. Our previous study demonstrated that the absence of transcript expression of ER β, but not of ER α, is significant in the postmenopausal vagina, which is in contrast to the results from this current study.[1] All these results demonstrate that, differential transcript expressions of ER subtypes occur in different postmenopausal tissues. Although both ER α and ER β bind with the same substrate (estrogen), ER β may mediate diverse functions at different sites for different menstural status through a different mechanism.[2,7] The results of the current study support the concept of selective estrogen receptor modulators and lend support to an alternative to hormone replacement therapy.[8,9]

From our results, we suggest mRNA expression for both ER subtypes in the uterine cervix does not differ significantly between proliferative and secretory phases. Whilst, Konish et al and Mosny et al[10,11] noted that, the ER content of the cervical squamous epithelium depends upon the menstrual cycle. Our study relates to the presence or absence of the mRNA expression in the cervical tissues; their studies, however, relied upon the ER content in different epithelial layers. By contrast, an investigation of ER β was not included in these studies which used immunohistochemical analysis for tissue identification and differed from our investigation which relied upon RT-PCR.

In addition, in order to compare the mRNA expression of each ER subtype according to menstrual status, we also studied the expression of these receptors for normal and carcinomatous tissues samples from the uterine cervix. We found that both ER α and ER β transcripts are expressed consistently for all normal sites from the seven cervical cancer samples. One carcinomatous sample revealed an absence of both ER subtype transcripts while a second was deficit only in ER β (Table 2). The ER α mRNA expression for normal sites from cervical cancer samples is 100% (7/7), while the ER α expression for carcinomatous sites is 85.7% (6/7). The ER β mRNA expression for normal sites from cervical cancer samples is 100%, while the ER β expression from carcinomatous portions is 71.4%. Although the absence of both ER α and ER β mRNA expression in carcinomatous areas from cervical cancer samples is more likely in comparison to normal areas, it does not reach statistical significance (Table 2), thus it is suggested that neither ER α nor ER β play a role in cervical carcinogenesis.

Our results show that there is no significant difference in mRNA expression for each ER subtype, when comapring carcinomatous and normal tissues. Mosny et al used an immunohistochemical method to demonstrate that ER staining was negative in the neoplastic squamous epithelium of the cervix.[11] Kanai et al further demonstrated that the expression of estrogen receptors in neoplastic lesions of the cervix was markedly decreased when using the immunohistochemical method.[12] The ER β expression was not studied in their research. Because the ER concentration is definitely higher

in cervical stroma tissue than in the squamous epithelium of the cervix[13-16]; in the analysis of ER in the cytosol of cell homogenates, which are not representative of the neoplastic cells, the stroma cells may cause an incorrectly positive result.[17] Thus, a high incidence of mRNA expression is produced, lowering the incidence of ER subtype expression loss for cervical cancers, which perhaps occurs in our study. We used RT-PCR, because we believed that the immunohistochemical method is not as sensitive as RT-PCR, with more ER expression loss resulting. Different cut-off levels for ER subtypes, which different studies define as negative in immunohistochemical method, may also explain different results for ER subtype expression loss in cervical cancer samples.

In conclusion, ER α mRNA expression differs significantly when comparing pre- and postmenopausal cervical samples, however, ER β mRNA expression is not changed in postmenopausal cervical samples. There is no difference in mRNA expression for each ER subtype in cervical samples for different phases of the menstrual cycle. These results suggest that hormone insufficiency and the tissue specific mechanisms mediated by ER α and ER β interact to control the expression of estrogen receptor subtypes. The authors suggest that these ER subtypes are perhaps not involved in cervical carcinogenesis because transcripts for both ER α and ER β are detected and not differentially expressed in the normal and carcinomatous areas of cervical cancer samples. Our results are preliminary and derived from a limited number of samples, the precise physiological and pathological roles of each ER subtype need further investigation.

計畫成果自評

本研究計畫原為二年期，但只申請到一年經費，故針對子宮頸甲、乙型動情素接受體之訊息核糖核酸之表現作比較。

本研究達成我們比較子宮頸甲、乙型動情素接受體於正常〈不同月經週期、停經期前後〉、和癌組織〈與其同一檢體正常組織比較〉之訊息核糖核酸表現的目的。

我們的結果是一嶄新發現，即子宮頸甲、乙型動情素接受體之訊息核糖核酸表現，於增殖、分泌期沒有差異；只有甲型動情素接受體牽涉到正常停經後子宮頸的變化；至於癌組織的變化可能都和兩種動情素接受體沒有關聯。目前這些新發現，尤其只有甲型動情素接受體牽涉到停經後子宮頸的變化，而乙型則沒有，可提供我們臨床上"selective estrogen receptor modulators"之應用。

本研究有新發現，可發表在期刊上。

綜合言之，本研究可提供一些有關停經和癌症的新發現，實有價值尋求經費做更廣、更深入研究。

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genital tract. Am J Pathol 1986;123:280-92.
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Table 1. Ages, parities, menstrual status and estrogen receptors alpha and beta mRNA expression in normal cervical samples of nineteen patients

Patients	Ages	Parities	Menstrual status	ER α *	ER β
1	52	3	Menopause	-	-
2	56	5	Menopause	-	-
3	57	4	Menopause	-	-
4	65	5	Menopause	-	-
A	43	5	Menopause	+	+
B	58	6	Menopause	+	+
5	39	2	Proliferative	-	+
6	46	4	Proliferative	+	+
7	45	0	Proliferative	+	+
8	44	3	Proliferative	+	-
C	42	3	Proliferative	+	+
9	39	3	Secretory	+	+
10	51	2	Secretory	+	-
11	43	3	Secretory	+	+
12	43	4	Secretory	+	-
D	40	1	Secretory	+	+
E	40	4	Secretory	+	+
F	43	5	Secretory	+	+
G	46	4	Secretory	+	+

ER α = estrogen receptor alpha

ER β = estrogen receptor beta

\+ ER subtype detected

\- ER subtype not detected

Patients 1-10: cases of uterine myoma

patients A-G: cases of cervical cancer.

* Fisher's exact test shows significant difference for the ER α mRNA expression in normal cervical samples between premenopausal and postmenopausal patients ($P < 0.05$), but no significant difference for the ER β mRNA expression. There is no significant difference for the mRNA expression of each ER subtype between proliferative and secretory cervical samples.

Table 2. Transcript expression of estrogen receptors alpha and beta in normal and carcinomatous sites from seven cervical cancer samples

Patients	Normal sites		Carcinomatous sites	
	ER α *	ER β #	ER α *	ER β #
Patient A	+	+	+	+
Patient B	+	+	+	-
Patient C	+	+	-	-
Patient D	+	+	+	+
Patient E	+	+	+	+
Patient F	+	+	+	+
Patient G	+	+	+	+

ER α = estrogen receptor alpha

ER β = estrogen receptor beta

\+ ER subtype detected

\- ER subtype not detected

*, # Fisher's exact test shows no significant difference for the mRNA expression of each ER subtype between normal and carcinomatous sites of uterine cervix.