行政院國家科學委員會專題研究計畫 期末報告

女性肺腺癌：雌激素-腫瘤壞死因子間之交互影響及雌激素受器的角色（GM07）

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 101-2629-B-400-001-
執 行 期 間 ：101 年 08 月 01 日至 102 年 07 月 31 日
執 行 單 位 ：財團法人國家衛生研究院環境衛生與職業醫學研究組

計 畫 主 持 人 ：李立安

計畫參與人員：碩士級-專任助理人員：邱哲豪

公 開 資 訊 ：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中 華 民 國 102 年 10 月 29 日

中 文 摘 要 ： 肺腺癌是台灣女性癌症死亡主要病因，雖然吸菸已知是導致肺癌的首要危險因子，流行病學研究顯示肺腺癌多為非吸煙者，且不吸菸的女性較男性更易罹患肺腺癌，雌激素與雌激素受器極可能在其中扮演某種角色。雌激素受器陽性肺腺癌細胞在雌激素刺激下，腫瘤壞死因子受器的表現上揚，繼而增強癌細胞對促炎激素「腫瘤壞死因子」的感度，促進下游NF-kB 轉錄功能的活化，引發發炎反應，影響癌症發展。

中文關鍵詞： 肺腺癌、雌激素受體、腫瘤壞死因子、訊息傳導、發炎反應

英 文 摘 要 ： Lung adenocarcinoma is a leading cause for female cancer deaths in Taiwan. Epidemiological evidence shows that female never smokers have a higher risk of lung adenocarcinoma than male counterparts. Estrogen signaling may play an important role in lung adenocarcinoma development and progression. Our studies found that estrogen receptor α (ERα)-positive lung adenocarcinoma cells expressed higher levels of tumor necrosis factor α (TNFα) receptor than ERα-negative adenocarcinoma cells under a physiological concentration of estrogen. Compared to ERα-negative adenocarcinoma cells, ERα-positive lung adenocarcinoma cells also exhibited a sharper dose-dependent response to TNFα in terms of NF-kB activation. Knockdown of ERα decreased TNFα-induced NF-kB activity. Antiestrogen fulvestrant could not suppress the stimulatory effect of ERα on TNFα-induced NF-kB activity. In contrast, fulvestrant enhanced TNFα-induced NF-kB activity as 17β-estradiol (E2). These results suggested that ERα facilitated TNFα to activate the NF-kB signaling pathway via a nongenomic action in addition to upregulation of TNFα receptor transcriptional expression. Activation of NF-kB in response to E2/TNFα cotreatment was accompanied with synergistic increase in expression of interleukin-8 (IL-8) and intracellular adhesion molecule 1(ICAM-1) involved in pulmonary inflammation.

英文關鍵詞： lung adenocarcinoma, estrogen receptor, TNFα, NF-kB signaling, inflammation

行政院國家科學委員會補助專題研究計畫 □期中進度報告 ■期末報告

女性肺腺癌：雌激素-腫瘤壞死因子間之交互影響及雌激素受器的角色

計畫類別：■個別型計畫　□整合型計畫
計畫編號：NSC 101－2629－B－400－001－
執行期間： 101 年 8 月 1 日至 102 年 7 月 31 日

執行機構及系所：財團法人國家衛生研究院環境衛生與職業醫學研究組

計畫主持人：李立安
共同主持人：
計畫參與人員：邱哲豪(研究助理)

本計畫除繳交成果報告外，另含下列出國報告，共 0 份：
□移地研究心得報告
□出席國際學術會議心得報告
□國際合作研究計畫國外研究報告

處理方式：除列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年■二年後可公開查詢

中　華　民　國 102 年 10 月 7 日

目　　錄

中文摘要

肺腺癌是台灣女性癌症死亡主要病因，雖然吸菸已知是導致肺癌的首要危險因子，流行病學研究顯示肺腺癌多為非吸煙者，且不吸菸的女性較男性更易罹患肺腺癌，雌激素與雌激素受器極可能在其中扮演某種角色。雌激素受器陽性肺腺癌細胞在雌激素刺激下，腫瘤壞死因子受器的表現上揚，繼而增強癌細胞對促炎激素「腫瘤壞死因子」的感度，促進下游 NF-kB 轉錄功能的活化，引發發炎反應，影響癌症發展。

中文關鍵詞：肺腺癌、雌激素受體、腫瘤壞死因子、訊息傳導、發炎反應

Abstract

Lung adenocarcinoma is a leading cause for female cancer deaths in Taiwan. Epidemiological evidence shows that female never smokers have a higher risk of lung adenocarcinoma than male counterparts. Estrogen signaling may play an important role in lung adenocarcinoma development and progression. Our studies found that estrogen receptor α (ERα)-positive lung adenocarcinoma cells expressed higher levels of tumor necrosis factor α (TNFα) receptor than ERα-negative adenocarcinoma cells under a physiological concentration of estrogen. Compared to ERα-negative adenocarcinoma cells, ERα-positive lung adenocarcinoma cells also exhibited a sharper dose-dependent response to TNFα in terms of NF-kB activation. Knockdown of ERα decreased TNFα-induced NF-kB activity. Antiestrogen fulvestrant could not suppress the stimulatory effect of ERα on TNFα-induced NF-kB activity. In contrast, fulvestrant enhanced TNFα-induced NF-kB activity as 17β-estradiol (E2). These results suggested that ERα facilitated TNFα to activate the NF-kB signaling pathway via a nongenomic action in addition to upregulation of TNFα receptor transcriptional expression. Activation of NF-kB in response to E2/TNFα cotreatment was accompanied with synergistic increase in expression of interleukin-8 (IL-8) and intracellular adhesion molecule 1(ICAM-1) involved in pulmonary inflammation.

Keywords: lung adenocarcinoma, estrogen receptor, TNFα, NF-kB signaling, inflammation

INTRODUCTION

Lung cancer is a leading cause for female cancer deaths in Taiwan, and about 70 % of female lung cancer cases are adenocarcinoma. Re-examining the distribution of females and males among nonsmoker patients documented in a number of epidemiological studies, Dr. Jill Siegfried found that the female to male ratio ranged from 1.25 to 5.21 and the ratio among the total cases was 2.46 (Siegfried, 2001). A large-scale nurse/health professional USA cohort study (1986-2000) also reported that nonsmoking women had a 33% higher incidence of lung cancer than nonsmoking men (Bain et al., 2004). High body estrogen probably predisposes women to lung adenocarcinoma.

The cellular response to estrogen is mainly mediated by estrogen receptor alpha (ERα) and beta (ERβ). ERβ expression was frequently detected in well and moderately differentiated lung adenocarcinoma specimens and correlated with better survival (Omoto et al., 2001; Kawai et al., 2005; Schwartz et al., 2005; Ali et al., 2008; Nose et al., 2009). In contrast, ERα expression in lung tumors remains inconclusive. While some studies reported no ERα expression detectable in lung tumors (Omoto et al., 2001; Schwartz et al., 2005; Wu et al., 2005), some suggested an association between positive ERα expression and poor prognosis (Kawai et al., 2005; Raso et al., 2009; Olivo-Marston et al., 2010). In addition, ERα expression was detected more frequently in tumors from females (Kaiser et al., 1996; Fasco et al., 2002; Raso et al., 2009). Inconsistence among laboratories in detection sensitivity and specificity probably contributes to the data discrepancy.

Aside from epidemiological association, our animal study indicated that estrogen promoted xenograft tumor growth of $ERα^+$ lung adenocarcinoma cells but inhibited that of $ERα^-$ cells. Estrogen-bound ERα probably influenced cancer development by regulation of transcription of cancer-related genes, e.g., *VEGF-A*, via binding to an estrogen responsive element (ERE) (Lin et al., 2012). Estrogen may also increase lung adenocarcinoma risk via a nongenomic action. 17β-estradiol (E_2) has been shown to rapidly activate cAMP, Akt, and MAPK signaling pathways in human lung adenocarcinoma 201T cells (Zhang et al., 2009).

Elevated TNFα level has been found in tumor tissues and serum of cancer patients (Ferrajoli et al., 2002; Szlosarek et al., 2006). Crosstalk between the estrogen and TNFα signaling pathways is relevant in carcinogenesis. A study reported there was an inverse correlation between the protein levels of ERα and the NF-kB subunits RelB in human breast cancer tissues and cell lines. RelB-induced Bcl-2 expression enhanced the invasive capability of ERα-negative breast cancer cells (Wang et al., 2006). In addition, TNFα was shown to antagonize E_2/ERα-induced cell proliferation by down-regulation of ERα in MCF-7 breast cancer cells. The TNFα-induced ERα down-regulation involved the PI3K/Akt pathway but not proteasome-dependent proteolysis (Lee and Nam, 2008). In U2OS osteosarcoma cells, estrogen repressed TNFα autoinduction by conversion of ERα from a transcriptional coactivator of NF-kB to a corepressor (Cvoro et al., 2006). ERα exhibited a direct protein-protein interaction with the NF-kB subunits p65, particularly in the presence of E_2 (Cvoro et al., 2006; Quaedackers et al., 2007). Positive crosstalk between estrogen and TNFα was also found. E_2/TNFα cotreatment caused a more than additive up-regulation of ~60 genes, including the anti-apoptotic BIRC3 gene, in breast cancer cells. Overexpression of the positive crosstalk gene set was associated with worse disease outcome (Frasor et al., 2009). We are interested in knowing how estrogen and TNFα crosstalk in ERα-positive and negative lung adenocarcinoma cells and whether the crosstalk affects tumor progression and transformation.

MATERIALS AND METHODS

Reporter Transfection Analysis

ER activity was determined by transiently transfection of cells with pERE-Luc and pSV40-βgal using Lipofectamine™ 2000 (Life Technologies), whereas NF-kB activity was assayed by infection with adenoviral NF-kB luciferase reporter. Cells were recovered overnight in phenol red-free RPMI-1640 medium (Sigma-Aldrich) plus 3% charcoal/dextran-treated fetal bovine serum (Life Technologies) followed by indicated treatments.

Gene Expression Analysis

RNA extraction and real-time RT-PCR was performed as described previously (Lin et al., 2012). Gene expression levels were normalized to β-actin expression levels. Gene specificity was confirmed by sequencing PCR products.

Immunoblotting.

Protein extraction and immunoblotting were performed as described previously (Kuo et al., 2013). Primary antibodies used in this study are mouse anti-ERα (D-12), anti-β-actin (C4) from Santa Cruz Biotechnology, and rabbit anti-TNFR1 (3736) from Cell Signaling Technology.

Statistical analysis.

Results are presented as mean ± SE. One-way ANOVA plus Turkey's post hoc test (SPSS) was used to calculate the significance of a difference.

RESULTS AND DISCUSSION

Construction of inducible ERα-expressing cell lines

In order to understand the impact of the estrogen signaling pathway on the response of lung adenocarcinoma cells to TNFα, we have constructed cell lines that conditionally express ERα by stable transfection of the tetracycline-regulated ERα expression system into the ERα-negative human lung adenocarcinoma CL1-5 cell line. Two daughter cell lines were selected based on Western blotting and reporter transfection. As shown in Figure 1A, ERα is highly expressed in each corresponding daughter line after a 24-h treatment with 1 μg/ml Dox (a tetracycline analogue). ERE-Luc reporter transfection showed that treating CL1-5(TO-ERα)#11 and #18 with 1 nM E2 (a physiological concentration in premenopausal women) for 24 h significantly increased the activity of the estrogen-responsive reporter in the presence of Dox (Fig. 1B), confirming that induction of ERα expression positively regulated the ERE-dependent transcriptional response to estrogen in these two transgenic cell lines.

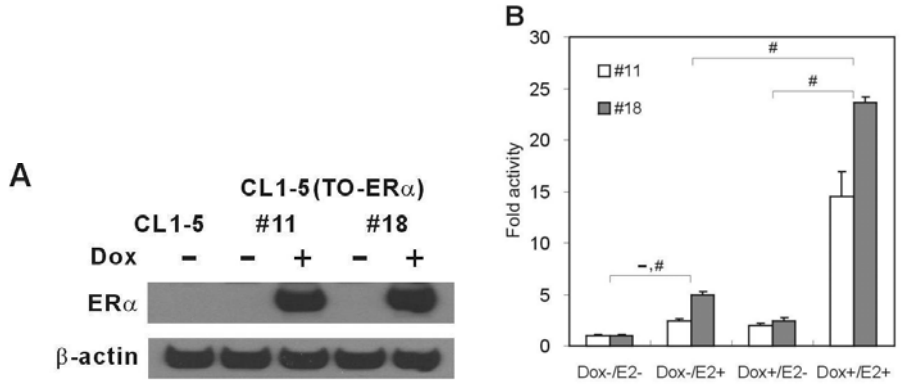

Figure 1. (A) ERα and β-actin protein expression in CL1-5 and daughter cell lines. ERα was highly expressed

in the CL1-5(TO-ERα) daughter lines 24 h after addition of 1 μg/ml Dox. (B) ERα activity under a variety of Dox (1 μg/ml) and E2 (1 nM) treatments for 24 h. # $p < 0.01$ between treatments.

Estrogen-inducible expression of TNF receptor in ERα-expressing lung adenocarcinoma cells

The cellular response to TNFα is initiated through the binding of TNFα to its receptor on the cell surface. We found that the primary form of TNFα receptor, TNFR1, was induced by E2 treatment (1 nM, 24 h) in ERα-expressing CL1-5(TO-ERα) cells at both mRNA and protein levels. The E2/ERα-induced TNFR1 up-regulation could be abolished by cotreatment with an ER antagonist, ICI 180,782 (10 nM) (Fig. 2).

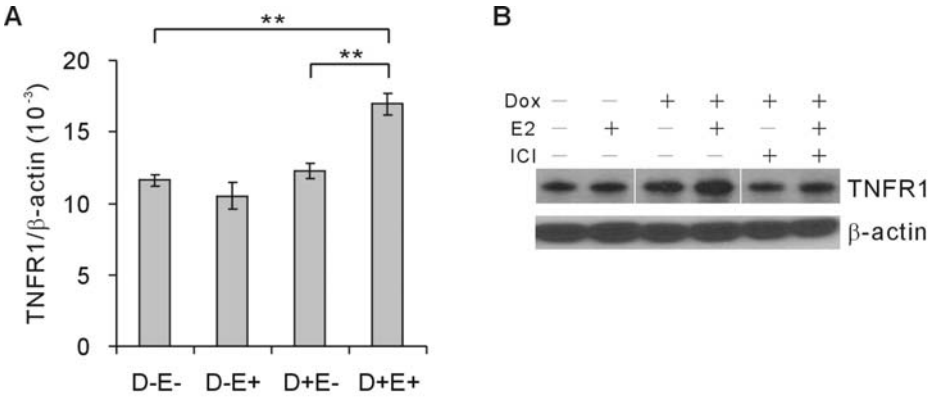

Figure 2. TNFR1 mRNA (A) and protein (B) expression in the absence and presence of ERα expression and E2 treatment. The house-keeping gene β-actin was employed as a normalization control. ** $p<0.005$.

Elevated NF-kB activity in ERα-expressing lung adenocarcinoma cells

Activation of NF-kB transcriptional activity is one of the most important events in response to TNFα signals. We assumed that TNFR1 up-regulation would enhance the responsiveness of cells to TNFα and, in turn, increase NF-kB activation. Reporter assay showed that NF-kB activity was significantly increased when ERα expression was induced by Dox pretreatment. Addition of E2 along with Dox further raised NF-kB activity. ICI 180,782 could not block the E2/ERα-enhanced NF-kB activation, Indeed, ICI 180,782 possessed similar positive effects on NF-kB activity as E2 (Fig 3). These data suggested that E2/ERα stimulated NF-kB activation not simply through up-regulation of the downstream estrogen-responsive genes, such as TNFR. The presence of ERα itself seemed to have nongenomic effects on NF-kB activation. Association with a ligand, either agonistic or antagonistic, facilitated the nongenomic action. Dox pretreatment lacked such positive effects on NF-kB activity in the parental CL1-5 cell line. Knockdown of ERα expression by RNA interference further validated the stimulation by ERα.

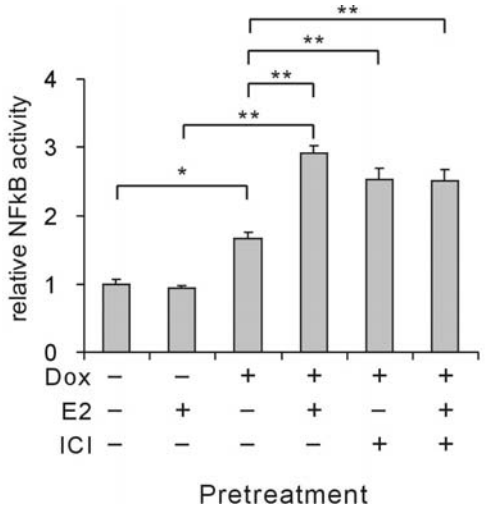

Figure 3. NF-kB reporter activity under various Dox/E2/ICI 180,782 treatments prior to a 4-h TNFα treatment. * $p<0.05$; ** $p<0.005$.

Up-regulation of inflammatory markers in company with increased NF-kB activity

Vast activation of NF-kB activity would lead to apoptosis or inflammation. We did not detect apoptosis. On the other hand, transcript levels of inflammatory markers, such as IL-8 and ICAM-1, were largely increased following the increase of NF-kB activity (Fig. 4). Elevated inflammatory response has been known to promote cancer progression.

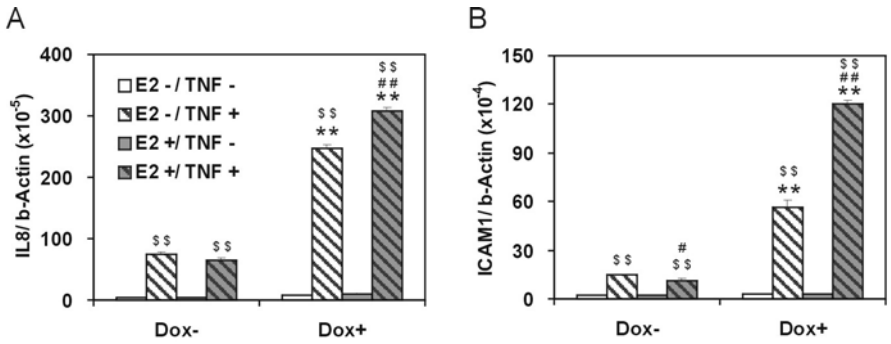

Figure 4. IL-8 (A) and ICAM-1 (B) mRNA expression in the absence and presence of ERα expression and E2 treatment. ** $p<0.005$ *vs*. Dox-; $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.005$ *vs*. E2-; $^{\$\$}$ $p<0.005$ *vs*. TNFα-.

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progesterone receptors identifies a subset of NSCLCs and correlates with EGFR mutation. Clin Cancer Res 15, 5359-5368.

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附錄

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□ 未達成目標（請說明，以 100 字為限）

□ 實驗失敗

□ 因故實驗中斷

□ 其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 □未發表之文稿 ■撰寫中 □無

專利：□已獲得 □申請中 □無

技轉：□已技轉 □洽談中 □無

其他：（以 100 字為限）

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）（以 500 字為限）

實驗發現雌激素受器表現與否影響肺腺癌細胞對腫瘤壞死因子的感受，在乳癌細胞與子宮內膜癌細胞，雌激素可經由雌激素受器抑制 NF-kB 活化反應，進而降低下游發炎因子如 IL-8 的表現，但我們的研究顯示，雌激素在肺腺癌細胞中有截然相反的影響。雌激素受器可藉由典型與非典型機制改變腫瘤發展，此可能說明為何女性吸菸率較男性低但肺腺癌罹患率卻相對的高。本研究有助闡明肺腺癌性別差異之機轉，唯有對致病機轉有所瞭解，方能策畫出有效防治策略。

國科會補助計畫衍生研發成果推廣資料表

日期:2013/10/29

國科會補助計畫	計畫名稱: 女性肺腺癌: 雌激素-腫瘤壞死因子間之交互影響及雌激素受器的角色 (GM07)
	計畫主持人: 李立安
	計畫編號: 101-2629-B-400-001- 學門領域: 性別主流科技計畫

無研發成果推廣資料

101 年度專題研究計畫研究成果彙整表

計畫主持人：李立安	計畫編號：101-2629-B-400-001-
計畫名稱：女性肺腺癌: 雌激素-腫瘤壞死因子間之交互影響及雌激素受器的角色 (GM07)	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	1	0	100%		
國外	論文著作	期刊論文	0	1	100%	篇	撰寫中
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	無

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 □未發表之文稿 ■撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

實驗發現雌激素受器表現與否影響肺腺癌細胞對腫瘤壞死因子的感受，在乳癌細胞與子宮內膜癌細胞，雌激素可經由雌激素受器抑制 NF-kB 活化反應，進而降低下游發炎因子如 IL-8 的表現，但我們的研究顯示，雌激素在肺腺癌細胞中有截然相反的影響。雌激素受器可藉由典型與非典型機制改變腫瘤發展，此可能說明為何女性吸菸率較男性低但肺腺癌罹患率卻相對的高。本研究有助闡明肺腺癌性別差異之機轉，唯有對致病機轉有所瞭解，方能策畫出有效防治策略。