行政院國家科學委員會專題研究計畫 成果報告

研究人類子宮頸癌細胞內 MZF1 基因的生物功能
研究成果報告(精簡版)

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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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研究人類子宮頸癌細胞內 MZF1 基因的生物功能

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中文摘要

關鍵字: 人類子宮頸癌、骨髓鋅拇指蛋白、細胞移動、細胞侵襲

人類子宮頸癌（Human Cervical cancer）會導致婦女死亡在發展中國家和全世界女性惡性腫瘤的第二順位。雖然大部分的研究報告指出人類乳突病毒(HPV)感染是導致人類子宮頸癌最嚴重的威脅。但是，證據顯示在人類子宮頸癌發展過程中，HPV 感染也不足以誘發惡性腫瘤形成和基因變化，因此，為了了解整個子宮頸癌的分子機轉，尋找具代表性的目標基因是必要的。

Myeloid Zinc Finger 1 (MZF1) 是鋅拇指蛋白中 Kruppel 家族成員之一，它本身是一個轉錄因子，主要來源是從慢性白血病患者的 cDNA library 所構築出來的。MZF1 基因通常表現在骨隨前驅細胞（bone marrow progenitor cells），正常分化完成的血液就無法測到 MZF1 基因的存在。MZF1 本身會參與造血細胞和腫瘤細胞的生長、分化和凋亡。最近有文獻指出過度表現 MZF1 會誘導一些腫瘤細胞移動和侵襲能力增加,主要是透過 Axl 基因的表現。但是，MZF1 在子宮頸癌形成過程扮演的生物功能，至今仍然未知

我們實驗結果證實 MZF1 會表現在 C33A 和 HeLa 細胞，但不表現在兩株高度增殖和侵襲的子宮頸癌細胞株(CaSki 和 SiHa 細胞)。因此我們送入 MZF1 載體到 CaSki 和 SiHa 細胞會造成細胞移動和侵襲能力下降，但不影響細胞生長能力；此外，我們採用 RT-PCR 證實過度表現 MZF1 會抑制 MMP-2、MMP-3 和 u-PA 的表現，但是對於其它基因則無影響(uPAR、FAK、RhoA 和 Rac1)，因此，我們認為 MZF1 在子宮頸癌內可能扮演腫瘤抑制者的角色。然而 MZF1 調控細胞移動和侵襲的分子機制仍需要更進一步的探討。

英文摘要

Key Word: Human cervical cancer, Myeloid Zinc Finger 1, Cell migration, Cell invasion

Cervical cancer is a leading cause of cancer death among women of developing countries and remains the second most common malignancy in women worldwide. Although studies have demonstrated that human papillomavirus (HPV) is the most important etiological agent, evidence shows that HPV infection alone is insufficient to induce malignant changes and that other genetic variations are important in the development of cervical cancer, Thus, the find to candidate target genes may be necessary to understand the molecular mechanism of malignant transformation of human cervical cancer.

Myeloid zinc finger 1 (MZF1) is a transcription factor of the Krüppel family proteins originally cloned from a cDNA library from a patient with chronic myeloid leukemia. MZF1 expression is both necessary for hematopoietic cell and tumor cell differentiation and critical to the regulation of cell proliferation and apoptosis. Recently, Some paper have been reported that overexpression of MZF1 was induced cell migration and invasion, it association with regulating Axl gene expression in human soild cancer cells. However, the biological function of MZF1 in cervical cancer progression is presently unknown.

Our study showed that MZF1 gene was highly expressed in C33A and HeLa cells, not in higher proliferation/invasion cells (CaSki and SiHa). Transfected with MZF-1 vector into CaSki and SiHa cells, then decreased cell migration/invasion ability, but not effect cell proliferation. Moreover, used RT-PCR assay to suggest that overexpression MZF1 were inhibited the mRNA level of MMP-2, MMP-3 and uPA, but not effect other gene expression (uPAR, FAK, RhoA and Rac1). Therefore, we believed the role of MZF1 may be a tumor suppressor in cervical cancer progression. However, the molecular mechanisms of regulation of migratory/invasive association gene expression by MZF1 require further more investigation.

前言(Introduction)

Cervical cancer is a leading cause of cancer death among women of developing countries and remains the second most common malignancy in women worldwide [1]. Although studies have demonstrated that human papillomavirus (HPV) is the most important etiological agent, evidence shows that HPV infection alone is insufficient to induce malignant changes and that other genetic variations are important in the development of cervical cancer [2]. Characterization of indentified molecular markers should help to disclose the molecular mechanisms underlying cervical carcinomas for diagnostic, prognostic, and therapeutic use.

Transcription factors frequently consist of modular elements that include a DNA-binding domain and one or more separable effector domains that may activate or repress transcriptional initiation. Although the majority of the conserved sequence motifs identified in transcription factors are associated with DNA binding, many transcription factors also contain extended motifs that mediate oligomerization to create an active complex. For example, in transcription factors that bind DNA as a dimer, the leucine zipper and helix-loop-helix motifs serve as dimerization domains and increase the potential for functional variation [3]. In other transcription factors, such as the helix-turn-helix motif (homeobox genes) [4], leucine zipperbasic DNA binding domain (c-myc, fos/jun) [5], and the zinc finger motif (steroid-thyroid hormone receptors) [6]. The zinc finger motif consists of 12 amino acids that form a loop anchored at the base by histidine and cysteine residues that coordinate a zinc atom. Many of the C2H2 zinc finger family members regulate growth and differentiation with specific mutations resulting in human disease[7-9]. Zinc-finger transcription factors play an important role in cellular commitment to specific lineages, proliferation and differentiation [10]. Several have been identified in hematopoietic cells and carcinoma cell [11]. For example, GATA-1, Egr-1 and other zinc-finger, which seem to determine the cell lineage of erythrocytes, macrophages and carcinoma [10.12].

MZF1(myeloid zinc finger1) is a C_2H_2 zinc finger transcription factor originally isolated from the peripheral blood leukocytes of a patient with chronic myelogenous leukemia [13]。There are two forms of MZF（MZF1, MZF-2）which seem to be produced by alterative use of two transcriptional initiation sites [14]. The MZF1 cDNA encodes a protein of 485 amino acids containing a serine- and threonine-rich amino terminal domain followed by 13 consensus Kriippel-type zinc finger motifs that are contiguous except for a 24-residue, proline-rich insertion between fingers 4 and 5 domains[13].

研究目的(Objectives)

The aim of this study was to characterize the biology function of MZF1 in cervical cancer, we set up the four cervical cancer cell lines as model to study the biological function of MZF1, which at last will hopefully provide useful information for future molecular mechanism of human cervical cancer therapy

文獻探討(Literature Review)

From several lines of evidence suggest that MZF1 has been implicated as have a role in granulopoiesis, apoptosis and oncogenesis. MZF1 is specifically expressed in myeloid leukemia cells and myeloid progenitor cells at the myelocyte and metamyelocyte stage from normal marrow and not in later stages [15.16]. The specificity for granulocyte differentiation is also supported by the fact that basal MZF1 expression increases in myeloid HL-60 cells induced to differentiate along the granulocyte pathway with retinoic acid or DMSO but not if they are induced down the monocyte/macrophage lineage with TPA [17]. Moreover, antisense MZF1 inhibits granulocyte colony formation from normal human marrow in vitro [16]. Two lines of evidence suggest that MZF1 functions to control cell proliferation: (1) When MZF1 is overexpressed in the murine myeloid cell line FDCP.1, the programmed cell death these cells normally undergo in the absence of IL-3 is inhibited [17]. Moreover, when FDCP.1 cells overexpressing MZF1 are injected into nude mice, tumors develop at the site of injection that express the MZF1 transgene. (2) Retroviral transduction of NIH 3T3 cells with MZF1 also results in a 'transformed' phenotype with the cells forming piled up foci [18]. Previously our data show that MZF1 transcriptionally regulates PKCα in human hepatocellular carcinoma [19], which is an important family of signaling molecules that regulate cell proliferation and transformation. MZF1 antisense oligonucleotide–pretreated SK-Hep-1 human hepatocellular carcinoma cells showed reduced PKCα expression, and antisense-treated cells s.c. implanted into nude mice exhibited lower tumor growth and prolonged formation time [20]. These studies suggest that dysregulated expression of MZF1 could contribute to oncogenesis. In contrary, Allgayer H et al offered that MZF1 induces invasion and in vivo metastasis in colorectal cancer, at least in part by regulating Axl gene expression [21]. However, the biology functional role of MZF1 in the development of cervical cancer has not previously been reported in the literature.

方法及材料(Material and Methods)

Cell Culture.

HPV18-positive HeLa cervical carcinoma cells, HPV16-positive CaSki and SiHa cervical carcinoma cells were cultivated with DMEM (Gibco BRL) supplemented with 10% fetal bovine serum (FBS), 100 units/ml penicillin G, and 100 ug/ml streptomycin (Sigma Chemicals Co., USA), and were incubated at 37 °C in a humidified atmosphere containing 5% CO_2 and 95% humidify.

RNA isolation and RT-PCR analysis.

Total RNA was isolated from cell specimens by the Trizol reagent method. The extract integrity was assessed by 1.5% agarose gel electrophoresis and RNA was visualized by ethidium bromide staining. The total amount of RNA was determined spectrophotometrically. RT-PCR assay was performed according to De Petro et al. [1998] with slight modifications. An aliquot of total RNA (5 μg) was reverse transcribed. The RT product (2 μl) was diluted with the PCR buffer to a final volume of 50 μl, containing 0.5 μM dNTPs and 0.5 unit of Super-Therm Taq DNA polymerase. PCR was performed on a GeneAmp PCR system 2700. The PCR products were analyzed by 1.5% agarose gel electrophoresis and direct visualization after EtBr staining. The agarose gels were scanned and analyzed using the Kodak

Scientific 1D Imaging System.

Western blotting.

The whole cell lysates were lysed with a lysing buffer (50 mM Tris/HCl (pH 7.4), 2 mM EDTA, 2 mM EGTA, 150 mM NaCl, 1 mM PMSF, 1 mM NaF, 1 mM sodium orthovanadate, 1% (v/v) 2-mercaptoethanol, 1% (v/v) Nonidet P40, 0.3% sodium deoxycholate). Each sample (40 μg) was subjected to 10% SDS-PAGE and blotted onto a polyvinylidene fluoride membrane (Millipore, Belford, MA). After blocking, the membrane was incubated with the specific antibody. The blots were then incubated with HRP-conjugated anti-mouse or anti-rabbit antibody at room temperature for 1 h. Proteins were detected by the enhanced chemiluminescence detection system. (Amersham Pharmacia Biotech, Piscataway, NJ).

Cell proliferation assay.

Cell proliferation was measured by the yellow tetrazolium MTT assay as was described previously. Cells were seeded in 24-well plates at a density of 1 x 104 cells/well and cultured overnight in DMEM containing 10% serum before the addition of the pcDNA or pcDNA-MZF1 and incubation for up to 1, 2 and 3 days. After treatment, the medium was replaced by fresh medium and the cells were incubated for 4 h with 5 mg/ml MTT, which was dissolved in 1 ml isopropanol and kept for 10 min. The optical density at 570 nm (A570nm) was determined using a spectrophotometer.

Flow cytometric analysis.

CaSki and SiHa cells were transfected with pcDNA or pcDNA-MZF1 for 48 h. 1×10^6 cells fixed in 70% ethanol at -20 ℃ for overnight, then washed with PBS and incubated for 30 mins at room temperature in PBS containing 100 mg/ml RNase A, 0.1% Triton X-100, 1 mM EDTA and 1.5 mg/ml propidium iodide. Cell-cycle analysis was performed on a FACSCalibur flow cytometer utilizing Cellquest software.

Migration and Invasion assays.

CaSki and SiHa cells were grown to confluence, and treated with pcDNA or pcDNA-MZF1. After 48 h, cells were detached by trypsinisation and washed three times in serum-free DMEM. In the migration assay condition, the cells were plated at 2×105 cells/well in serum-free DMEM in the upper chamber of a 48–well Boyden chamber, which was plated with the 8-μm pore size polycarbonate membrane filters for 2 h before the cells were added. The cells were followed incubation for 6 hrs at 37 ℃ in a humidified 5% CO2 atmosphere. The Invasion assays were performed in the same manner as for migration assay, except the filter were precoated with Matrigel, and cells were incubated for 8 h at 37 ℃ in 5% CO_2 humidified condition as described previously. Cells were then fixed with methanol and stained with 0.05% Giema in distilled water. Cells of the upper surface of the filter were removed with a cotton swab and the filters were rinsed in distilled water until no addition stain leached and were air-dired for 20 mins. For each membrane, a total of 4 fields were selected at random, and the numbers were averaged.

結果與討論(Results and Discussion)

本實驗我們採用四株不同的子宮頸癌細胞 (C33A、HeLa、CaSki 和 SiHa) 來分析 MZF1 蛋白和 mRNA 表現，根據我們的採用 western blotting 和 RT-PCR 實驗證實 MZF1 蛋白和 RNA 會大量表現在 C33A 和 HeLa 細胞內，但不表現在 SiHa 和 CaSki 細胞 **(Fig-1)**。之前的文獻指出 SiHa 和 CaSki 的生長速率、移動和侵襲能力較強，而且我們初步結果也證實 MZF1 在 CaSKi 和 SiHa 細胞內幾乎無表現，因此想要更進一步了解過度表現 MZF1(overexpression MZF1)是否會影響細胞生長、移動和侵襲能力。我們短暫送入 MZF1 基因到 CaSki 和 SiHa 細胞內作用 24 和 48 小時，然後利用 MTT assay 證實 overexpression MZF1 並不影響 CaSki 和 SiHa 細胞生長速率**(Fig-2)**，此外，採用 flow cytometry 和 DAPI 染色更加確定 overexpression MZF1 並不會造成細胞凋亡**(Fig-3 和 Fig-4)**。接下來，我們短暫送入 MZF1 到 CaSki 和 SiHa 細胞內作用 48 小時，然後利用 migration/invasion assay 證實 overexpression MZF1 會造成 CaSki 和 SiHa 細胞移動和侵襲能力下降**(Fig-5)**。有文獻指出細胞移動和侵襲過程需要 MMP family 和細胞骨架蛋白參與，我們採用 RT-PCR 分析細胞移動和侵襲相關基因 mRNA 表現，實驗結果證實 MZF1 轉殖到 SiHa 細胞內會造成 MMP-2、MMP-3 和 u-PA 的表現下降**(Fig-6)**，但是對於其它基因則無影響(uPAR、FAK、RhoA 和 Rac1)，但是之後的研究還是會繼續分析 CaSki 細胞送入 MZF1 基因對於細胞移動和侵襲相關基因 mRNA 表現是否與 SiHa 細胞的結果一致。因此，綜合以上結果我們認為 overexpression MZF1 不會影響子宮頸癌生長，但是會抑制子宮頸癌的移動和侵襲能力，所以我們認為 MZF1 在子宮頸癌內可能扮演腫瘤抑制者(tumor suppressor)的角色。

根據我們的研究成果顯示過度表現 MZF1 在人類高度惡化子宮頸癌細胞 SiHa 和 CaSki 細胞證實會抑制細胞移動和侵襲能力。此外,我們 RT-PCR 結果也證實過度表現 MZF1 會抑制 MMP-2 和 uPA 的表現**(Fig-6)**。過去有文獻指出 SiHa 和 CaSki 細胞內會大量表現 MMP2，因而導致細胞移動和侵襲能力增強(22)，但是 uPA 則無報導。另一方面，本實驗採用 MZF1 基因本身是一個轉錄因子，且 MZF1 在不同癌細胞就有不同的生物功能，因此我們推測 MZF1 會調控 MMP2 和 uPA 的轉錄作用因而抑制細胞移動和侵襲能力。我們目前也在收集子宮頸癌檢體來驗證 MZF1、MMP2 和 uPA 之間的臨床資料比對，希望未來釐清 MZF1 在人類子宮頸癌扮演的角色。

Fig-1. 分析 MZF1 蛋白在四株子宮頸癌細胞表現

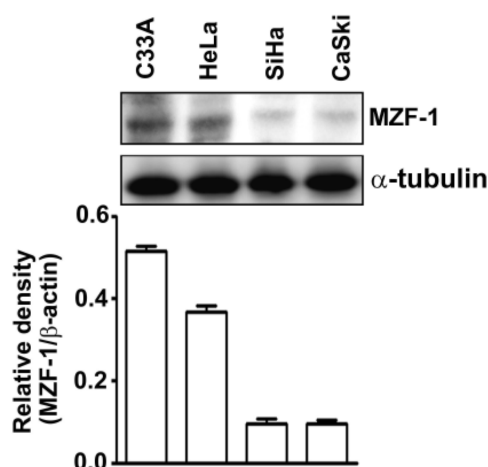


Fig-2 利用基因轉殖方式證實送入不同濃度 MZF-1 到 CaSki 和 SiHa 細胞的表現

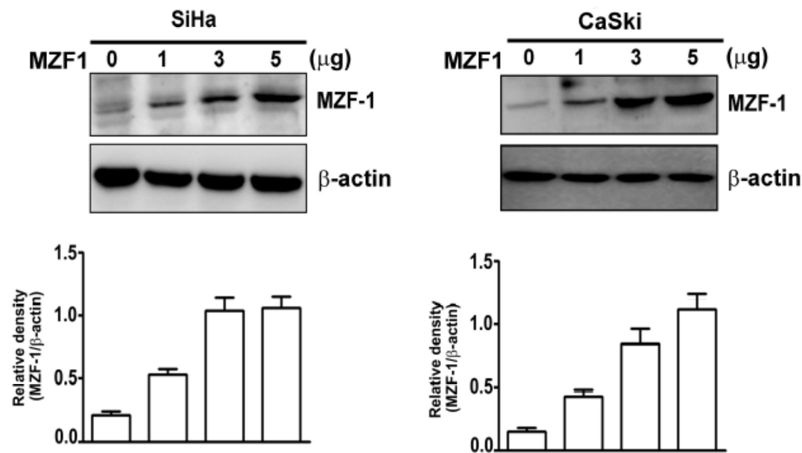


Fig-3 Overexpression MZF1 不影響子宮頸癌細胞存活率

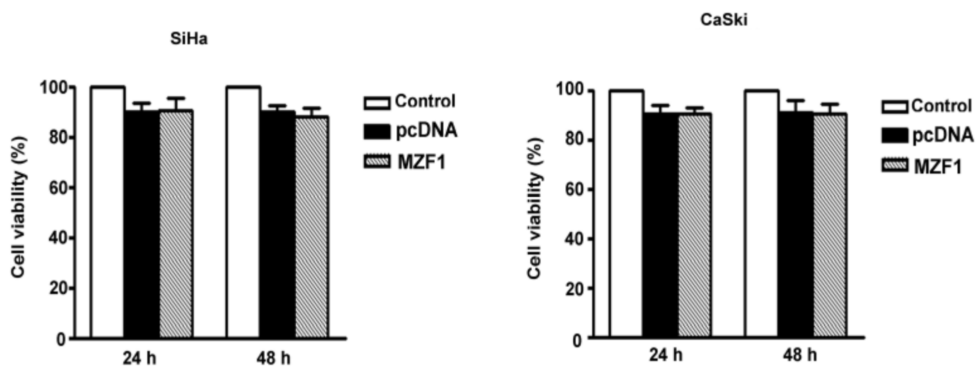


Fig-4. Overexpression MZF1 不影響子宮頸癌細胞凋亡

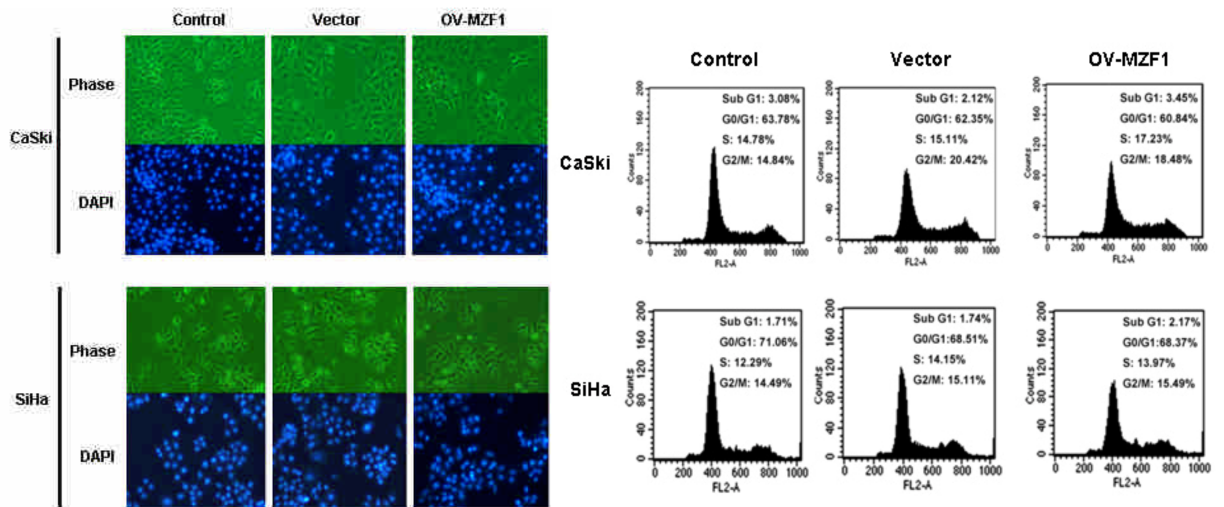


Fig-5. Overexpression MZF1 影響細胞移動和侵襲能力

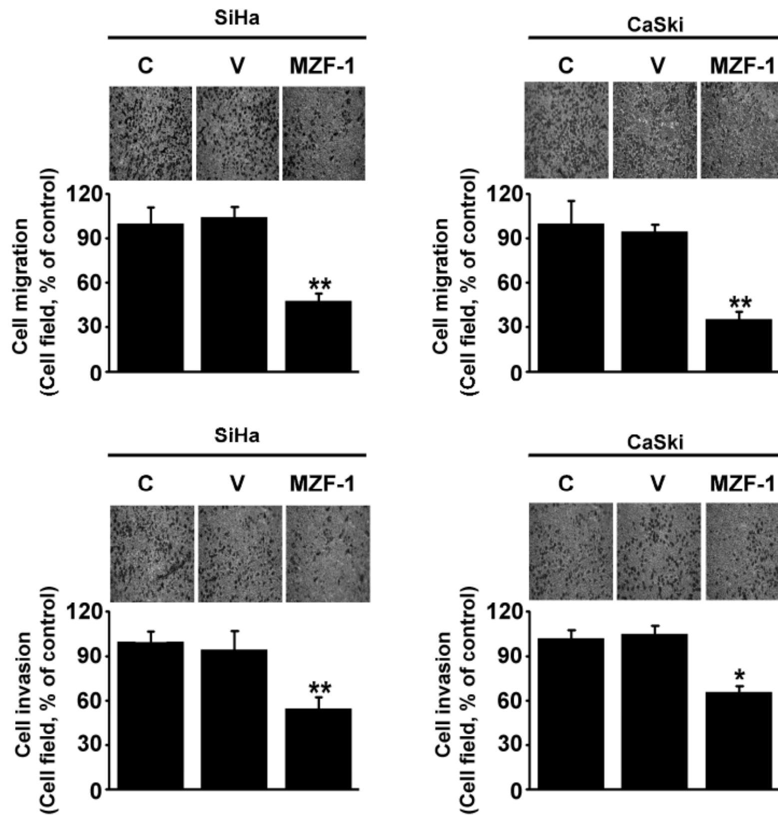
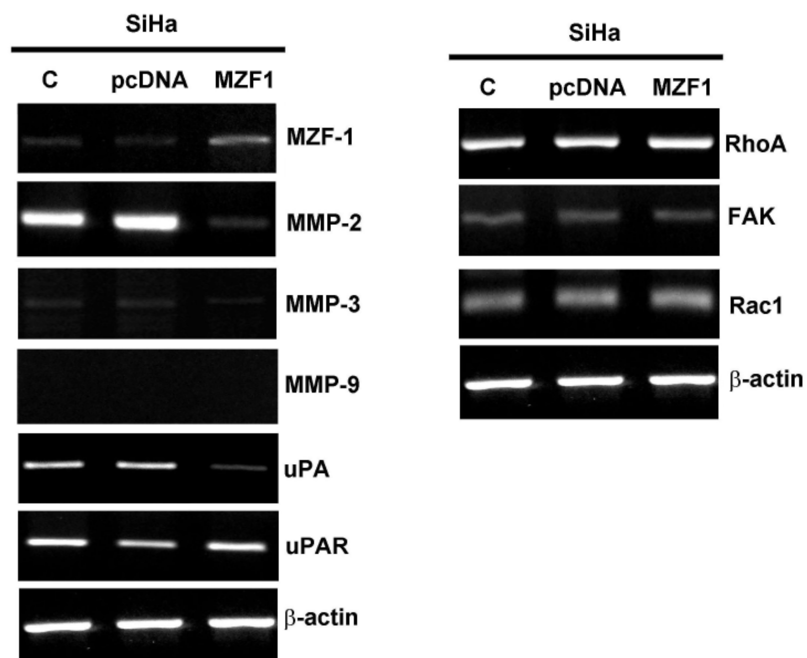


Fig-6. Overexpression MZF1 抑制細胞移動和侵襲相關基因



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無研發成果推廣資料

98 年度專題研究計畫研究成果彙整表

計畫主持人：應宗和 | **計畫編號：**98-2314-B-040-024-

計畫名稱：研究人類子宮頸癌細胞內 MZF1 基因的生物功能

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	無
		研究報告/技術報告	0	0	100%		無
		研討會論文	0	0	100%		無
		專書	0	0	100%		無
	專利	申請中件數	0	0	100%	件	無
		已獲得件數	0	0	100%		無
	技術移轉	件數	0	0	100%	件	無
		權利金	0	0	100%	千元	無
	參與計畫人力（本國籍）	碩士生	0	0	90%	人次	1 人參與
		博士生	0	0	100%		無
		博士後研究員	0	0	100%		無
		專任助理	0	0	100%		無
國外	論文著作	期刊論文	0	1	100%	篇	
		研究報告/技術報告	0	0	100%		無
		研討會論文	0	0	100%		無
		專書	0	0	100%	章/本	無
	專利	申請中件數	0	0	100%	件	無
		已獲得件數	0	0	100%		無
	技術移轉	件數	0	0	100%	件	無
		權利金	0	0	100%	千元	無
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	無
		博士生	0	0	100%		無
		博士後研究員	0	0	100%		無
		專任助理	0	0	100%		無

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）

學術意義:

人類子宮頸癌會導致婦女死亡在發展中國家和全世界女性惡性腫瘤的第二順位。雖然大部分的研究報告指出人類乳突病毒(HPV)感染是導致人類子宮頸癌最嚴重的威脅。但是，證據顯示在人類子宮頸癌發展過程中，HPV 感染也不足以誘發腫瘤形成和基因變化，為了了解整個子宮頸癌的分子機轉，尋找具代表性的目標基因是必要的。本實驗初步數據證實 MZF1 基因在人類子宮頸癌細胞是扮演抑制侵襲和移動角色,且與一些細胞移動和侵襲的指標蛋白有關聯性.此項學術結果是第一個發現MZF1 在子宮頸癌的生物功能可能是抑制腫瘤侵襲的角色。

進一步發展可能性:

未來希望著重 MZF1 在 in vivo 實驗(動物實驗)和子宮頸癌檢體之間做臨床數據的比較.另外將進一步來了解 MZF1 調控 MMP2 和 uPA 的轉錄活性機制,此項結果將可以更了解子宮頸癌內 MZF1 基因調節的分子機制.