科技部補助專題研究計畫成果報告
期末報告

髓系鋅指基因(MZF1)在口腔癌致癌過程的表現及其機制探討

計 畫 類 別 ：個別型計畫
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計 畫 主 持 人：林巧雯
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中 華 民 國 103 年 10 月 22 日

中 文 摘 要 ： Myeloid zinc finger (MZF1)基因屬於C2H2鋅手指轉錄因子中Kruppel家族裡的一員，並可透過調控protein kinase C的表現來影響許多人類癌細胞。而MZF1的表現與口腔癌之間的相關性目前仍須進一步的研究。本研究利用tissue microarrays (TMA)偵測274個口腔鱗狀細胞癌OSCC病人檢體中其MZF1的表現與患者臨床病理參數及其他預後因子的相關性。結果發現69.3%的OSCC患者其細胞核之免疫組織染色呈現MZF1陽性。在腫瘤細胞核無MZF1表現會和較高的癌症分期（p = 0.002）和較大的腫瘤相關（p < 0.001），但與淋巴結轉移及遠端轉移則無相關性。各項臨床參數經Cox proportional hazard regression以單變項分析，依腫瘤所在不同部位區分，在舌癌病人中，腫瘤細胞核無MZF1表現影響病人存活的危險率高達1.918倍（p = 0.030）。根據我們的實驗結果，在OSCC病人免疫組織染色中核的MZF1表現或許可以做為口腔癌的預後指標。

中文關鍵詞： MZF1， 口腔癌

英 文 摘 要 ： Myeloid zinc finger 1 (MZF1) is a zinc finger transcription factor belonging to the kruppel family protein which transcriptionally regulates protein kinase C expression in various human cancers. However, MZF1 expression in oral squamous cell carcinoma (OSCC) and its correlation with patients' prognosis have not been investigated so far. In this study, we detected the expression of MZF1 in 274 patients with OSCC by tissue microarrays (TMA), and evaluated its correlation with clinicopathologic factors and disease prognosis. Nuclear MZF1 expression was present in 190/274 (69.3%) cases and loss of nuclear expression of MZF1 was associated with more advanced clinical stages (p=0.002) and larger tumor size (p<0.001), but not associated with positive lymph node metastasis and distal metastasis. Importantly, loss of nuclear MZF1 expression correlated with poorer patient prognosis in univariate (p=0.030, log-rank test) survival analysis. According to our results, the nuclear expression of MZF1 in OSCC samples can predict the progression of OSCC and the survival of OSCC patients.

英文關鍵詞：

Expression of Myeloid zinc finger 1 and correlation to clinical aspects of oral squamous cell carcinoma by tissue microarray

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Abstract

Myeloid zinc finger 1 (MZF1) is a zinc finger transcription factor belonging to the kruppel family protein which transcriptionally regulates protein kinase C expression in various human cancers. However, MZF1 expression in oral squamous cell carcinoma (OSCC) and its correlation with patients' prognosis have not been investigated so far. In this study, we detected the expression of MZF1 in 274 patients with OSCC by tissue microarrays (TMA), and evaluated its correlation with clinicopathologic factors and disease prognosis. Nuclear MZF1 expression was present in 190/274 (69.3%) cases and loss of nuclear expression of MZF1 was associated with more advanced clinical stages (p=0.002) and larger tumor size (p<0.001), but not associated with positive lymph node metastasis and distal metastasis. Importantly, loss of nuclear MZF1 expression correlated with poorer patient prognosis in univariate (p=0.030, log-rank test) survival analysis. According to our results, the nuclear expression of MZF1 in OSCC samples can predict the progression of OSCC and the survival of OSCC patients.

Introduction

Currently, oral cancer is the fifth-most frequently occurring cancer worldwide

and the fourth-highest cause of male cancer mortality in Taiwan. More than 90% of all oral malignancies are squamous cell carcinomas (SCCs) [1]. The high prevalence of oral cancer in Taiwan has been attributed to the high rate of people who habitually chew betel quid [2]. Approximately half of oral SCCs affect the tongue and floor of the mouth [3]. There are 3 main treatment procedures for oral cancer: surgery, chemotherapy, and radiation therapy. Despite advances in surgical techniques and adjuvant therapies, the 5-year overall survival rate for patients after a diagnosis of oral SCC remains poor [4]. The search for potential prognostic markers is still being studied.

The myeloid zinc finger 1 (MZF1) is a zinc finger transcription factor of the kruppel family proteins originally cloned from the peripheral leukocytes of a patient with chronic myelogenous leukemia [5]. The gene encodes a 485-amino acid protein containing 13 C2H2 zinc fingers that are arranged in 2 distinct DNA-binding domains recognized as 2 independent DNA target sequences [6]. MZF1 plays a critical role in regulating the early stage of myeloid progenitor cell differentiation, including HL60, KG1, HEL, and K562 human leukemia cells [5]. Transient or constitutive MZF1 expression inhibits hematopoietic development by downregulating both CD34 and c-myb promoter activity [7]. In addition, MZF1 transcriptionally regulates protein kinase C α expression in various human cancers cells, such as human hepatocellular carcinoma cells, breast cancer cells and bladder transitional cell carcinoma cells [8-10]. Hsieh et al. have shown that treating the *antisense* oligodeoxynucleotides of MZF1 in human HCC cells inhibits cell migration, invasion, and tumor growth in nude mice [11]. In another study, overexpression of MZF1 induced metastasis in a solid tumor by increasing Axl-promoter activity [12]. However, Tsai et al indicated that MZF1 inhibits matrix metalloproteinase-2 transcription and reduces the

invasiveness of human cervical cancer cells [13]. These observations suggest that MZF1 plays multiple roles in tumorigenesis, functioning as both a tumor promoter and tumor suppressor. However, the biological roles of MZF1 in oral cancer remain poorly understood. In this study, we conducted an immunohistochemical analysis to investigate the relationships between the expression of MZF1 and clinicopathologic parameters in 274 patients with oral SCC.

Materials and Methods

Patients and samples

In this study, we enrolled 274 patients with oral cancer who had undergone surgical resection between 2000 and 2006. The clinical stages and grades for each patient were classified according to the TNM classification system and the World Health Organization classification system, respectively. The histopathologic and clinical manifestations were retrospectively observed for all patients. The outcome data and overall survival were collected from patient charts. This study was approved by the internal review board of the Chung Shan Medical University Hospital.

Tissue microarrays

Representative cancer specimens were selected from hematoxylin and eosin–stained sections and confirmed by the pathologists. One tissue core (2 mm in diameter) was obtained from each paraffin block from which cancerous tissues was cut longitudinally. The tissue cores were set into new paraffin blocks using a fine steel needle to produce the tissue microarrays.

Analyses of MZF1 expression by immunohistochemistry

The paraffin-embedded cancerous tissue sections (4 μm) was deparaffinized in xylene and rehydrated in alcohol. Endogenous peroxidase activity was blocked by 3% H_2O_2. Antigen retrieval was performed by treatment with boiling citrate buffer (10 mmol/L) for 20 minutes. After incubation with the antihuman MZF1 antibody (sc-46179, 1:200 dilution; Santqa Cruz Biotechnology, Santa Cruz, CA) for 20 minutes at room temperature and thorough washing (3 times with phosphate-buffered saline), the slides were incubated with a horseradish peroxidase/Fab polymer conjugate for another 30 minutes. The sites of peroxidase activity were visualized using 3,3′-diamino-benzidine tetrahydrochloride as the substrate and hematoxylin as the counterstain. Paraffin-embedded sections of normal colonic epithelium with homogeneous MZF1 nuclear staining were included as the positive controls. In the negative control, the primary antibody was omitted and replaced by phosphatebuffered saline. Nuclear expression of MZf1 was regarded as positive staining. The staining intensity in the cancerous tissue was graded on a scale from 0 to 2 according to the relative expression intensity compared with noncancerous oral squamous mucosa. MZF1 staining was scored as “2+” if the staining intensity in the cancer matched the staining intensity of the noncancerous oral squamous mucosa. The staining was scored as “1+” if the staining intensity in the cancer was lower than the staining intensity of the noncancerous oral squamous mucosa. A score of “0” reflected a lack of MZF1 immunoreactivity compared with the staining pattern of noncancerous oral squamous mucosa. All immunohistochemical staining cases were examined by 2 pathologists, and a final agreement was obtained for each score, even for discrepant immunostaining results.

Statistical analysis

MZF1 expression was assessed based on the intensity of the immunohistochemical staining. The primary outcome was overall survival, which was defined as the time from the initiation of surgery to death as a result of any cause or to the date of the last follow-up. Significant differences in the clinicopathologic variables between each group were tested using the Chi Square Test. The distribution of overall survival was estimated using a Kaplan-Meier plot and the log-rank test. The prognostic significance of the variables was evaluated using the Cox regression model and hazard ratios. The variables in the model included nuclear expression of MZF1, tumor grade, disease stage, T status, and lymph node metastasis. The analyses were performed using the SPSS Statistical Package (SPSS, Chicago, IL), and p value of less than 0.05 (2-tailed test) was considered statistically significant.

Results

Table 1 lists the clinicopathologic characteristics of patients with oral SCC. In this retrospective study, we enrolled 274 patients (259 men, 15 women) and analyzed their conditions. The patients were aged from 31 to 90 years (mean age = 55.85 ± 11.14 y). The cancers were located at the following sites: buccal mucosa (*n* = 105), tongue (*n* = 91), gingiva (*n* = 35), palate (*n* = 16), floor of the mouth (*n* = 14), and others (*n* = 13). Among the patients, 18.2% were at Stage I (*n* = 50), 20.4% were at Stage II (*n* = 56), 12.4% were at Stage III (*n* = 34), and 48.9% were at Stage IV (*n* = 134). All patients were classified according to the seventh edition of the TNM staging system. According to the level of nuclear MZF1 expression, we divided MZF1 immunohistological stains into two groups: positive

(1+/2+) and negative (0) stain (Figure 1). Nuclear MZF1 expression was present in 190/274 (69.3%) cases (Table 2). Our results revealed nonsignificant statistical differences between MZF1 nuclear expression and age, gender, cancer location, lymph node metastasis, distant metastasis, and grade. Patients with negative nuclear MZF1 expression were associated with more advanced clinical stages ($P = .002$) and a larger tumor size ($P < .001$). A univariate cox proportional hazard regression analysis of all oral SCC patients ($n = 274$) revealed that clinical stage ($P < .001$), tumor size ($P < .001$), and lymph node metastasis status ($P < .001$) were adverse prognostic factors for patients with oral cancer (Table 3). However, negative nuclear MZF1 expression was identified as a significant and independent prognostic factor ($P = .30$) only for patients with oral tongue squamous cell carcinoma ($n = 91$). We performed a Kaplan–Meier analysis to evaluate the relationship between the expression of MZF1 and overall survival (Figure 2). The results showed that oral tongue squamous cell carcinoma patients with negative nuclear MZF1 expression had a significantly lower survival rate ($P = .028$). The median survival in negative nuclear MZF1 expression was 28.8 months, whereas that in positive nuclear MZF1 expression was 78.6 months.

Discussion

Oral cancer has recently become a critical topic in Taiwan because the proportion of betel quid chewers is high [14]. Other risk factors for oral cancer include tobacco use, alcohol consumption, and human papilloma virus infection [15]. Oral cancer in Taiwan most frequently occurs on the tongue and buccal mucosa; cancer development at these sites is attributable to the habit of chewing betel quid [16,17]. Tissue biopsies are performed to diagnose oral cancer, which is typically

identified by advanced symptoms such as persistent bleeding. Despite advancements in therapy for patients with early-stage oral cancer, OSCC is still characterized as recurrent and involves a risk of tumor metastasis to cervical lymph nodes [18]. In this study, we evaluated MZF1 protein expression through immunohistochemistry, revealing that loss of nuclear MZF1 expression in patients with squamous cell carcinoma of the tongue is significantly associated with decreased overall survival rates.

MZF1 belongs to the Kruppel family of C2H2 zinc finger transcription factors, which are preferentially expressed in myeloid progenitor cells [5]. At least 3 isoforms of MZF1 proteins produced through alternative splicing have been reported [19,20]. MZF1 has been shown to play a vital role in regulating gene transcription, repressing transcription in nonhematopoietic cells, and activating transcription in cells of hematopoietic origin [21,22]. Evidence that the highest mRNA levels in HL60 cells induced by treatment with retinoic acid, dimethyl sulfoxide, and granulocyte-macrophage colony stimulating factor (GM-CSF) stimulate granulocytic differentiation indicates that MZF1 regulates hematopoietic development [5]. Similar results obtained by Bavisotto et al. showed that treated MZF1 antisense oligonucleotides in bone marrow cells significantly inhibited GM-CSF -driven granulocyte colony formation in vitro [20]. However, constitutive MZF1 expression negatively regulates CD34 and c-myb promoter activity in hematopoietic and nonhematopoietic cells upon the binding of MZF1 to regulatory elements in the 5’-flanking region of both genes [7]. These observations suggest that MZF1 acts as a genetic regulator of the cascade of gene expression during myeloid differentiation. In addition, MZF1 and Sp1/Sp3 upregulate N-cadherin promoter activity, and N-cadherin controls the expression of phenotypic genes in osteoblasts [23]. Previous

studies have determined the relationship between MZF1 and tumorigenesis. MZF-1 was overexpressed in poorly differentiated human HCC cells and was essential for cell migration and invasion because it upregulated PKCα [8]. Mudduluru et al. revealed that MZF1 binds to the Axl promoter, transactivating promoter activity and promoting the metastatic potential of colorectal and cervical cancer cells [12]. In addition, MZF1 that binds to an ErB2-responsive enhancer element in the first intron of CTSB activates the signaling network of cysteine-cathepsin-mediated invasiveness [24]. A recent study revealed that MZF1-mediated MYC expression caused by wild-type-LKB1 loss promotes tumor progression in lung adenocarcinoma cells [25]. However, the role of MZF1 in tumorigenesis remains disputed. An in vivo study using *Mzf1*$^{-/-}$ mice determined that MZF1 regulates the proliferative ability of hemopoietic cells participating in tumor growth and suppression [26]. Tsai et al. indicated that MZF1 binds to the promoter region of MMP2 and represses MMP2 transcription activity. The effect of MMP2 repression may be linked to inhibition of the migration potential of human cervical cancer cells [13].

In this study, we performed immunohistochemical analysis and observed that negative nuclear expression of MZF1 was associated with advanced clinical stage and a larger tumor size in patients with OSCC. In addition, loss of MZF1 expression significantly related to poor overall survival according to the results of Kaplan-Meier analysis. These results indicate that nuclear MZF1 is a potential biomarker for overall survival and OSCC progression.

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Table 1. Patient characteristics

Characteristics	Total (%)
Total number of patients	**274**
Age (year)	
Mean ± SD	55.83 ± 11.14
Gender	
Male	259(94.5%)
Female	15 (5.5%)
Cancer location	
Buccal mucosa	105 (38.3 %)
Tongue	91 (33.2 %)
Gingiva	35 (12.8 %)
Palate	16 (5.8 %)
Floor of Mouth	14 (5.1 %)
Others	13 (4.7 %)
Clinical stage	
I	50 (18.2%)
II	56 (20.4%)
III	34 (12.4%)
IV	134 (48.9%)
T classification	
T1	67 (24.5%)
T2	88 (32.1%)
T3	22 (8.0%)
T4	97 (35.4%)
N classification	
N0	172 (62.8%)
N1	35 (12.8%)
N2	63 (22.9%)
N3	4 (1.5%)
M classification	
M0	271 (98.9%)
M1	3 (1.1%)
Grade	
Well	41 (15.0%)
moderate, poor	233 (85.0%)
Chemotherapy	
No	197 (71.9%)
Yes	65 (23.7%)
Unknown	12 (4.4%)
Radiotherapy	
No	95 (34.7%)
Yes	167 (60.9%)
Unknown	12 (4.4%)

Table 2. Patient characteristics regarding nuclear MZF-1 expression

	No. of patients (%)		
Characteristics	MZF-1 (-)	MZF-1 (+)	p value
Total number of patients	84 (30.7)	190 (69.3)	
Age (year)			
<55	43 (51.2)	94 (49.5)	0.793
≥55	41 (48.8)	96 (50.5)	
Gender			
Male	81 (96.4)	178 (93.7)	0.357
Female	3 (3.6)	12 (6.3)	
Cancer location			
Buccal mucosa	35 (41.7)	70 (36.8)	0.818
Tongue	25 (29.8)	66 (34.7)	
Gingiva	10 (11.9)	25 (13.2)	
Others	14 (16.6)	29 (15.3)	
Clinical stage			
I	6 (7.1)	44 (23.2)	**0.002***
II+III+IV	78 (92.9)	146 (76.8)	
T classification			
T1	8 (9.5)	59 (31.1)	**<0.001***
T2+T3+T4	76 (90.5)	131 (68.9)	
N classification			
N0	49 (58.3)	123 (64.7)	0.312
N1+2+3	35 (41.7)	67 (35.3)	
M classification			
M0	82 (97.6)	189 (99.5)	0.174
M1	2 (2.4)	1 (0.5)	
Grade			
Well	14 (16.7)	27 (14.2)	0.599
moderate, poor	70 (83.3)	163 (85.8)	
Chemotherapy			
No	54 (67.5)	143 (78.6)	0.056
Yes	26 (32.5)	39 (21.4)	
Radiotherapy			
No	23 (28.8)	72 (39.6)	0.094
Yes	57 (71.3)	110 (60.4)	

*$p<0.05$

Table 3. Univariate survival analyses of MZF-1 and clinicopathological parameters among patients with oral cancer using the Cox proportional hazard regression model

All cases (N=274)	**Hazard ratio (95% CI)**	**p value**
Clinical stage (stage 1 + 2 versus stage 3 + 4)	2.498 (1.732–3.602)	< 0.001*
T status (T1 + T2 versus T3 + T4)	1.778 (1.291–2.450)	< 0.001*
N status (N0 versus N1 + N2 + N3)	2.833 (2.049–3.917)	< 0.001*
M status (M0 versus M1)	2.666 (0.848–8.380)	0.093
Cytoplasmic MZF-1 (+ versus -)	1.133 (0.818–1.570)	0.452
Nuclear MZF-1 (+ versus -)	1.193 (0.851–1.672)	0.306

Buccal mucosa (N=105)	**Hazard ratio (95% CI)**	**p value**
Clinical stage (stage 1 + 2 versus stage 3 + 4)	2.918 (1.596–5.336)	0.001*
T status (T1 + T2 versus T3 + T4)	1.676 (0.966–2.909)	0.066
N status (N0 versus N1 + N2 + N3)	4.154 (2.374–7.269)	< 0.001*
M status (M0 versus M1)	2.937 (0.400–21.547)	0.289
Cytoplasmic MZF-1 (+ versus -)	1.286 (0.743–2.226)	0.368
Nuclear MZF-1 (+ versus -)	0.911 (0.509–1.631)	0.753

Tongue (N=91)	**Hazard ratio (95% CI)**	**p value**
Clinical stage (stage 1 + 2 versus stage 3 + 4)	2.197 (1.177–4.102)	0.013*
T status (T1 + T2 versus T3 + T4)	1.848 (1.044–3.273)	0.035*
N status (N0 versus N1 + N2 + N3)	2.262 (1.277–4.007)	0.005*
M status (M0 versus M1)	1.470 (0.202–10.678)	0.704
Cytoplasmic MZF-1 (+ versus -)	1.316 (0.745–2.324)	0.344
Nuclear MZF-1 (+ versus -)	1.918 (1.064–3.456)	0.030*

*$p<0.05$

Figure 1

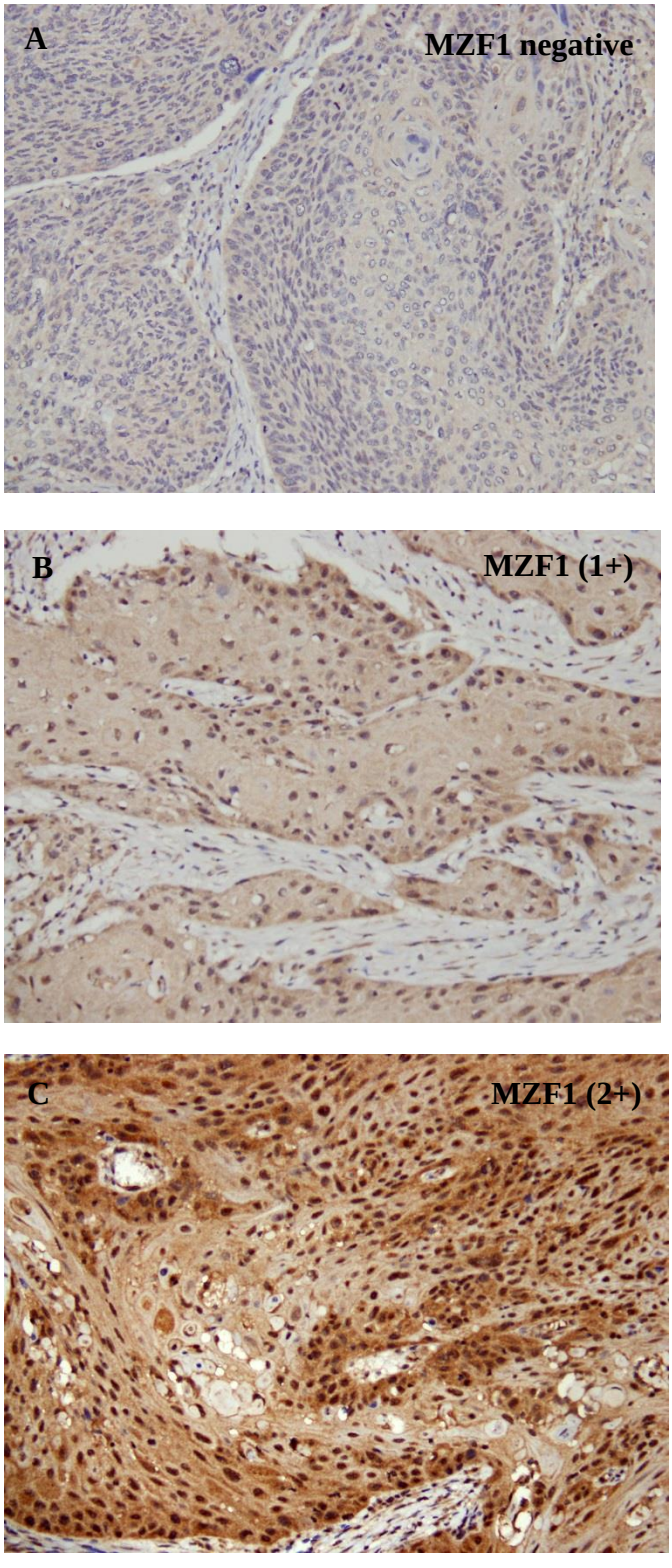
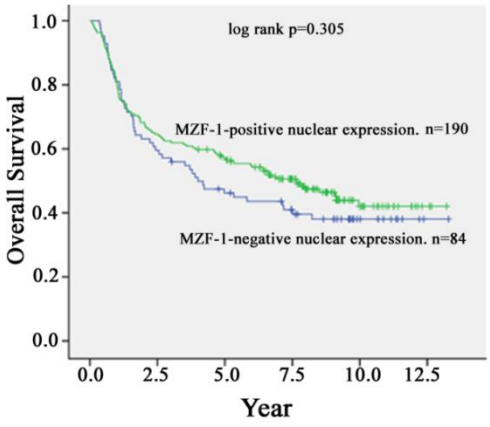
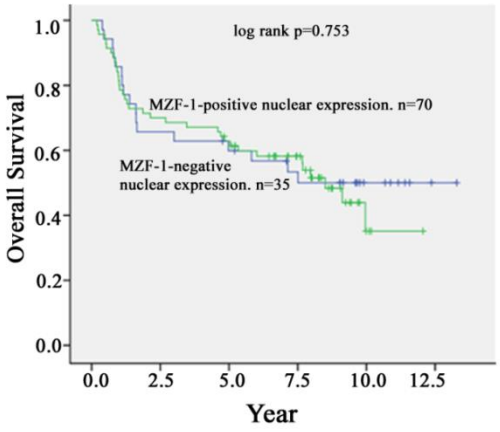


Figure 2.

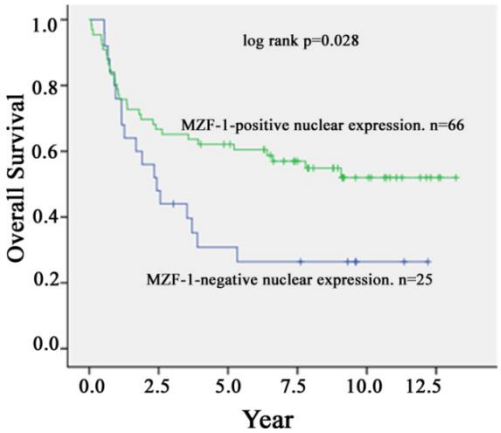
(A) Overall n=274



(B) Buccal mucosa n=105



(C) Tongue n=91



科技部補助計畫衍生研發成果推廣資料表

日期:2014/10/22

科技部補助計畫	計畫名稱: 髓系鋅指基因(MZF1)在口腔癌致癌過程的表現及其機制探討
	計畫主持人: 林巧雯
	計畫編號: 102-2314-B-040-011- 學門領域: 牙醫學

無研發成果推廣資料

102 年度專題研究計畫研究成果彙整表

計畫主持人：林巧雯	計畫編號：102-2314-B-040-011-
計畫名稱：髓系鋅指基因(MZF1)在口腔癌致癌過程的表現及其機制探討	

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	1	1	100%	人次	
		博士生	1	1	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	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	1	1	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	

科技部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）

Myeloid zinc finger (MZF1)基因屬於 C2H2 鋅手指轉錄因子中 Kruppel 家族裡的一員，並可透過調控 protein kinase C 的表現來影響許多人類癌細胞。而 MZF1 的表現與口腔癌之間的相關性目前仍須進一步的研究。本研究利用 tissue microarrays (TMA)偵測 274 個口腔鱗狀細胞癌 OSCC 病人檢體中其 MZF1 的表現與患者臨床病理參數及其他預後因子的相關性。結果發現 69.3% 的 OSCC 患者其細胞核之免疫組織染色呈現 MZF1 陽性。在腫瘤細胞核無 MZF1 表現會和較高的癌症分期 ($p = 0.002$) 和較大的腫瘤相關 ($p < 0.001$)，但與淋巴結轉移及遠端轉移則無相關性。各項臨床參數經 Cox proportional hazard regression 以單變項分析，依腫瘤所在不同部位區分，在舌癌病人中，腫瘤細胞核無 MZF1 表現影響病人存活的危險率高達 1.918 倍 ($p = 0.030$)。根據我們的實驗結果，在 OSCC 病人免疫組織染色中核的 MZF1 表現或許可以做為口腔癌的預後指標。