科技部補助專題研究計畫成果報告
期末報告

新穎基因第六型表皮生長因子類蛋白在口腔癌致癌過程的表現及其調控癌症轉移之機制探討(第2年)

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中 文 摘 要 ： EGFL6 (epidermal growth factor-like domain multiple-6)又稱為MAEG，過去的研究已鑑識出其位於人類染色體圖譜Xp22的位置並且在胎兒組織與早期發育中大量表現。近來的研究發現EGFL6大量表現在類骨細胞 (osteoblastic-like cells) 並且透過啟動胞外訊息調節激酶 (Extracellular signal-regulated kinase, ERK) 訊號路徑誘發內皮細胞的細胞遷徙(cell migration)及血管新生作用(angiogenesis)。EGFL6基因被觀察到大量表現於卵巢癌 (ovarian cancer)，在卵巢腫瘤相關內皮細胞的 EGFL6 基因表現量相對於正常對照來說顯著增加了 36.8倍 。然而EGFL6的表現與口腔癌之間的關聯性仍然尚未明瞭。本研究針對392位口腔鱗狀上皮癌(oral squamous cell carcinoma, OSCC)的患者以酵素免疫分析法 (Enzyme-Linked ImmunoSorbent Assay, ELISA) 分析患者血漿中的EGFL6表現量，發現當患者具有較大的腫瘤體積 (T status, p =0.002)，遠端轉移 (distant metastasis, p = 0.001)，還有較高的TNM分期 (p = 0.033) 時，血漿中的EGFL6具有顯著較高的表現量。因此，EGFL6除了參與OSCC的致癌物作用(carcinogenesis)之外，在臨床應用上也或許可以作為OSCC患者的腫瘤標記(biomarker)。

中 文 關 鍵 詞 ： EGFL6, 口腔鱗狀上皮癌, 酵素免疫分析法

英 文 摘 要 ： Abstract:
EGF-like domain 6 (EGFL6), a member of the epidermal growth factor (EGF) repeat protein superfamily, is a secreted protein that promotes endothelial cell migration and angiogenesis. The current study investigated the association between the clinicopathological characteristics and plasma level of EGFL6 in patients with oral squamous cell carcinoma (OSCC). We measured the plasma EGFL6 levels of 392 OSCC patients by using a commercial enzyme-linked immunosorbent assay. We also analyzed EGFL6 mRNA levels of 328 OSCC patients from The Cancer Genome Atlas (TCGA) dataset. The results showed that plasma EGFL6 levels were significantly higher in patients with OSCC than in healthy controls ($p < 0.001$). Similar results were observed for the TCGA bioinformatics database. Moreover, plasma EGFL6 levels were significantly higher in the patients with advanced T status ($p = 0.002$), distant metastasis ($p = 0.001$), and higher TNM stage ($p=0.033$). In conclusion, our results suggest that plasma level of EGFL6 may be useful to assess disease progression, and especially advanced T status and higher TNM stage in patients with OSCC.

英 文 關 鍵 詞 ： EGFL6,OSCC,ELISA

High Level of Plasma EGFL6 Is Associated with Clinicopathological Characteristics in Patients with Oral Squamous Cell Carcinoma

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Short Title: Plasma EGFL6 in oral cancer

Abstract

EGF-like domain 6 (EGFL6), a member of the epidermal growth factor (EGF) repeat protein superfamily, is a secreted protein that promotes endothelial cell migration and angiogenesis. The current study investigated the association between the clinicopathological characteristics and plasma level of EGFL6 in patients with oral squamous cell carcinoma (OSCC). We measured the plasma EGFL6 levels of 392 OSCC patients by using a commercial enzyme-linked immunosorbent assay. We also analyzed EGFL6 mRNA levels of 328 OSCC patients from The Cancer Genome Atlas (TCGA) dataset. The results showed that plasma EGFL6 levels were significantly higher in patients with OSCC than in healthy controls ($p < 0.001$). Similar results were observed for the TCGA bioinformatics database. Moreover, plasma EGFL6 levels were significantly higher in the patients with advanced T status ($p = 0.002$), distant metastasis ($p = 0.001$), and higher TNM stage ($p=0.033$). In conclusion, our results suggest that plasma level of EGFL6 may be useful to assess disease progression, and especially advanced T status and higher TNM stage in patients with OSCC.

Keywords: EGFL6, oral squamous cell carcinoma, biomarker

Introduction

Both genetic and environmental factors contribute to the development of oral cancer, and major risk factors include the use of tobacco products, betel nut chewing, and alcohol consumption [1-3]. Approximately 90% of oral cancers are squamous cell carcinomas, and oral squamous cell carcinoma (OSCC) is the tenth most common cancer worldwide and the fourth most common cancer among men in Taiwan [4-6]. It is also the most common malignancy of the head and neck region, accounting for 2–4% of all cancer cases in Western countries and more than 10% in some areas of Asia [7, 8]. The 5-year relative survival rate of OSCC is unfavorable even with aggressive interventions, because invasion of the neighboring tissues and metastasis to the neck lymph nodes are common [9]. Identifying new biomarkers that can predict the risk of OSCC progression, especially local invasion and metastasis, are needed to improve the control of this deadly cancer.

Tumor invasion and metastasis are related to a series of complex processes, including cell adhesion, migration, invasion, angiogenesis, and anchorage-independent growth [10-15]. In addition, degradation of the extracellular matrix (ECM) giving cancer cells access to blood vessels and lymphatics is also a key process. The epidermal growth factor (EGF) repeat superfamily features a series of conserved cysteines and glycines positioned in a domain of 30 to 40 residues [16]. EGF-like proteins are characterized by their multiple EGF repeats [17]. EGF-like repeat family members are predominantly

secreted as cell surface molecules, and are often involved in the regulation of the cell cycle, proliferation, and developmental processes [18, 19]. The binding of EGF-like proteins to their receptors triggers a wide range of biological functions, including proliferation, differentiation, apoptosis, adhesion, and migration [17]. EGF motif-containing molecules have been previously linked to the progression of various cancers [20, 21], and the expression of EGF-like domain 6 (EGFL6) in tumors suggests that it may also be linked to cancer [22-25].

The EGFL6 protein is a member of the EGF repeat superfamily which is secreted and then promotes endothelial cell migration and angiogenesis [26]. EGFL6 has been shown to be expressed in fetal tissues and pancreatic, lung, ovarian and breast tumors [20, 27-29]. In microarray-based detection and expression analysis of ECM proteins in drug-resistant ovarian cancer cell lines, the over-expression of EGFL6 has been observed in the WITR cell line [28]. Since EGFL6 is expressed specifically in certain tumors but not in normal adult tissues, the EGFL6 gene product represents a potential marker of malignancy [20]. However, the potential expression and role of EGFL6 in patients with OSCC have yet to be elucidated. In this study, we investigated the association between the clinicopathological characteristics and plasma level of EGFL6 in patients with OSCC.

Materials and Methods

Subjects and specimen collection

We recruited 392 patients with OSCC (mean age 55.33±10.93 years) at Chung Shan Medical University Hospital in Taichung and Changhua Christian Hospital in Changhua, Taiwan between 2008 and 2015. OSCC were clinically staged at the time of diagnosis according to the TNM staging system of the American Joint Committee on Cancer (AJCC) Staging Manual, seventh edition. Medical information of the OSCC patients including TNM clinical staging, primary tumor size, lymph node involvement, and histological grade was obtained from their medical records. Whole blood samples were collected from the patients and placed in tubes containing ethylene diamine tetraacetic acid. After immediate centrifugation at 3000 rpm, the supernatants were stored at -80℃. Before conducting this study, approval from the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH No: CS13214-1; CSMUH No: CS15150) and informed written consent to participate in the study were obtained from each patient.

Quantitative analysis of plasma EGFL6 level

The plasma EGFL6 concentration was determined quantitatively using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Human EGFL6 Immunoassay E01E0401; BlueGene Biotech, Shanghai,

China). One hundred microliters of plasma sample (100-fold dilution), standard control sample and internal quality control were placed into microtiter plates coated with a monoclonal antibody against EGFL6 and incubated for 2 hours at room temperature on a horizontal orbital shaker at 200 rpm. The absorbance was measured at 450 nm by using a microtest plate spectrophotometer (BioTek Instruments, Vemont, USA). EGFL6 levels were quantified with a calibration curve using human EGFL6 as the standard.

Statistical analysis

The demographic data are presented as number (%) and mean ± standard deviation (SD). Significances of differences between means were calculated using the Student's t-test. In addition, gender, smoking status, alcohol consumption status and betel nuts chewing status were analyzed using the x2 test. A p value less than 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 16.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Three hundred and ninety-two patients with OSCC were included in the analysis.

Table 1 presents the demographic data, and shows that 88.3% of the patients were smokers, 51.5% consumed alcohol, and 78.3% chewed betel nuts. The TNM status and types of tumor cell differentiation of the patients are also shown in Table 1.

Correlation between plasma EGFL6 levels and clinicopathological characteristics of the patients

The mean plasma EGFL6 level was significantly higher in patients with OSCC than in controls (304.48 ± 194.55 pg/mL vs. 178.69 ± 102.96 pg/mL; $p < 0.001$) (Figure 1A). To verify our findings, TCGA OSCC database was used in this study. Samples filtered involved only six oral cancer subtypes (alveolar ridge, base of tongue, buccal mucosa, floor of mouth, oral cavity, oral tongue; filtered oral cancer dataset size: n = 328). The EGFL6 mRNA levels of OSCC and normal tissues were evaluated. Figure 1B shows the EGFL6 mRNA levels were also significantly higher in patients with OSCC tissues than in normal tissues (Figure 1B). Moreover, the EGFL6 expression was also significantly increased in cancer tissue compared with that in the normal parts in OSCC of the TCGA database (Figure 1C).

The relationships between plasma EGFL6 levels and various clinicopathological parameters of the patients are summarized in Table 2. Plasma levels of EGFL6 protein were not correlated with age, gender, smoking, drinking, betel nuts chewing, lymph node

metastasis or cell differentiation. However, they were significantly higher in the patients with higher TNM stage (stage III + stage IV; p = 0.033), advanced T status (T3+T4; p = 0.002) and distant metastasis (M1; p = 0.001). Detailed comparisons of plasma EGFL6 levels between the patients with different disease severity are illustrated in Figure 2. With regards to TNM stage, the levels of EGFL6 were significantly higher in the patients with stage IV (332.83 pg/mL) compared to those with an early stage (stage I: 274.22 pg/mL) (Figure 2). The levels of EGFL6 were significantly higher in the patients with advanced tumor T status (T4: 347.73 pg/mL) compared to those with early T status (T1: 273.67 pg/mL and T2: 286.64 pg/mL; p=0.004 and p=0.020) (Figure 3).

Discussion

The advantage of using plasma tumor markers is that plasma can easily be obtained before treatment and at any time during follow-up without the necessity to invasively acquire tissue. It is clinically invaluable to have biomarkers which can provide information regarding the likelihood of a high TNM stage. This is particularly important in the context of patients with OSCC because their outcomes are closely related to disease progression and prognosis. Reliable tumor markers for these patients would therefore assist in assessing the prognosis and prediction of tumor behavior and in

planning adequate therapy.

In this study, we investigated the levels of EGFL6 in 392 OSCC patients, and found that elevated plasma levels of EGFL6 were correlated with advanced T status, distant metastasis and high TNM stage. EGFL6 protein levels were significantly higher in patients with advanced T status (T3+T4; $p = 0.002$), distant metastasis (M1; $p = 0.001$), and higher TNM stage (stage III + stage IV; $p=0.033$). Previous reports have shown that tumor invasion and metastasis are related to cell adhesion, migration, invasion, angiogenesis, and anchorage-independent growth [10, 30-34]. In addition, the EGFL6 protein has been reported to induce cell migration and angiogenesis of endothelial cells [26, 35-38]. These findings may explain our results, and suggest that EGFL6 may promote OSCC tumor invasion and metastasis by promoting cell migration and angiogenesis. Our results also suggest that EGFL6 may play an important role in the carcinogenesis of OSCC.

Several EGF-like superfamily members have been identified, including EGFL2, EGFL3, EGFL5, EGFL6, EGFL7, EGFL8, and EGFL9. EGFL2, EGFL5 and EGFL9 contain transmembrane domains, however EGFL3, EGFL6, EGFL7and EGFL8 lack transmembrane domains and are secreted as proteins [26]. The EGFL6 gene maps to the human Xp22 chromosome and encodes a secreted protein containing multiple EGF repeat motifs, which is highly expressed in certain tumors and fetal tissues, suggesting a role as

a growth factor [27, 39]. Using RNA *in situ* hybridization, the expression of EGFL6 has been detected in several sites, including all of the dermatome derivatives including the dermis of the trunk, hair follicles, and mesenchyme of the cranio-facial region [40].

Previous studies have reported that the EGFL6 protein induces migration and angiogenesis of endothelial cells [35-38], but that endothelial cells themselves do not express EGFL6 [26]. Several signaling pathways during angiogenesis have been reported to be potentially activated, such as the integrin/FAK-mediated pathway, MAPK pathway, and the PIK3/Akt pathway [35, 41, 42]. Chim et al [26] reported that extracellular signal-regulated kinase (ERK) is activated by the EGFL6 protein, and that inhibition of the ERK signaling pathway blocks EGFL6-induced ERK activation and endothelial cell migration. They further validated that EGFL6 promotes endothelial cell migration and angiogenesis via activation of the ERK pathway [26].

In addition to oral cancer, the overexpression of plasma EGFL6 has been observed in several tumors including brain, lung, ovarian, and breast tumors, but generally not in normal adult tissues [27-29] . EGFL6 has also been proposed to be a new target for diagnostic and therapeutic interventions in patients with breast cancer, which shows promise for new areas of basic research in tumor biology [29]. Combined with our results, the plasma level of the EGFL6 protein appears to be a likely candidate biomarker for various human cancers.

To the best of our knowledge, this is the first report to examine the association between plasma EGFL6 level and clinicopathological characteristics for patients with OSCC with regards to the possible application of this molecule as a tumor marker. We suggest that EGFL6 may play an important role in the carcinogenesis of OSCC, and that this may have an important implication in the treatment of patients with OSCC. The detection of the EGFL6 protein in the plasma may serve as tumor marker to predict the likelihood of OSCC in patients without the disease.

In summary, we found that a substantial increase in the plasma level of EGFL6 by ELISA is useful to assess disease progression, especially in patients with OSCC with an advanced T status and higher TNM stage. As a secreted protein, EGFL6 may not only play an important role in the carcinogenesis of OSCC, but also find clinical applications as a biomarker for disease diagnosis and in planning therapy for patients with OSCC.

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Table 1. Demographic characteristics and clinical features of OSCC patients.

Variables	OSCC (n = 392)
Age (years)	55.33 ± 10.93
Gender: male (%)	385 (98.2%)
Smoking status	
No	46 (11.7%)
Yes	346 (88.3%)
Drinking status	
No	190 (48.5%)
Yes	202 (51.5%)
Betel nuts chewing	
No	85 (21.7%)
Yes	307 (78.3%)
EGFL6 (pg/mL)	304.48 ± 194.55
Stage	
I	103 (26.3%)
II	67 (17.1%)
III	42 (10.7%)
IV	180 (45.9%)
Tumor T status	
T1	124 (31.6%)
T2	109 (27.8%)
T3	33 (8.4%)
T4	126 (32.1%)
Lymph node status	
N0	253 (64.5%)
N1	46 (11.7%)
N2	90 (23.0%)
N3	3 (0.8%)
Metastasis	
M0	390 (99.5%)
M1	2 (0.5%)
Cell differentiation	
Well differentiated	57 (14.5%)
Moderately or poorly differentiated	335 (85.2%)

Table 2. Correlation between plasma levels of EGFL6 and clinicopathological parameters in 392 OSCC patients.

Variables	No. of case (%) n = 392	EGFL6 level Mean ± S.D. (pg/mL)	p value
Age (years)			
<55	182 (46.4%)	303.25 ± 192.82	0.907
≥55	210 (53.6%)	305.55 ± 196.49	
Gender			
male	385 (98.2%)	304.81 ± 195.85	0.802
female	7 (1.8%)	286.17 ± 105.22	
Smoking status			
No	46 (11.7%)	283.02 ± 135.87	0.427
Yes	346 (88.3%)	307.33 ± 201.04	
Drinking status			
No	190 (48.5%)	314.45 ± 191.09	0.326
Yes	202 (51.5%)	295.10 ± 197.76	
Betel nuts chewing			
No	85 (21.7%)	275.86 ± 140.22	0.126
Yes	307 (78.3%)	312.40 ± 206.58	
Stage			
I+II	170 (43.4%)	280.63 ± 186.88	**0.033***
III+IV	222 (56.6%)	322.74 ± 198.71	
Tumor T status			
T1+ T2	233 (59.4%)	279.74 ± 175.98	**0.002***
T3+T4	159 (40.6%)	340.73 ± 214.39	
Lymph node status			
N0	253 (64.5%)	297.42 ± 185.82	0.333
N1+N2+N3	139 (35.5%)	317.34 ± 209.59	
Metastasis			
M0	390 (99.5%)	302.19 ± 191.46	**0.001***
M1	2 (0.5%)	751.21 ± 371.22	
Cell differentiation			
Well differentiated	57 (14.5%)	338.69 ± 39.65	0.151
Moderately or poorly differentiated	335 (85.2%)	298.66 ± 170.44	

*p<0.05.

Figure 1A

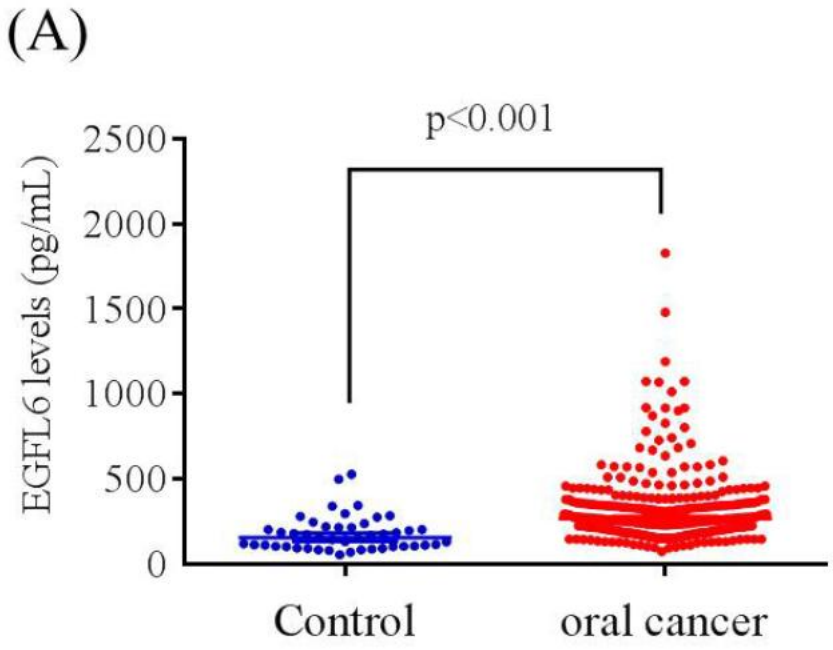

Figure 1A. EGFL6 levels were compared according to normal control and OSCC patients.

Figure 1B

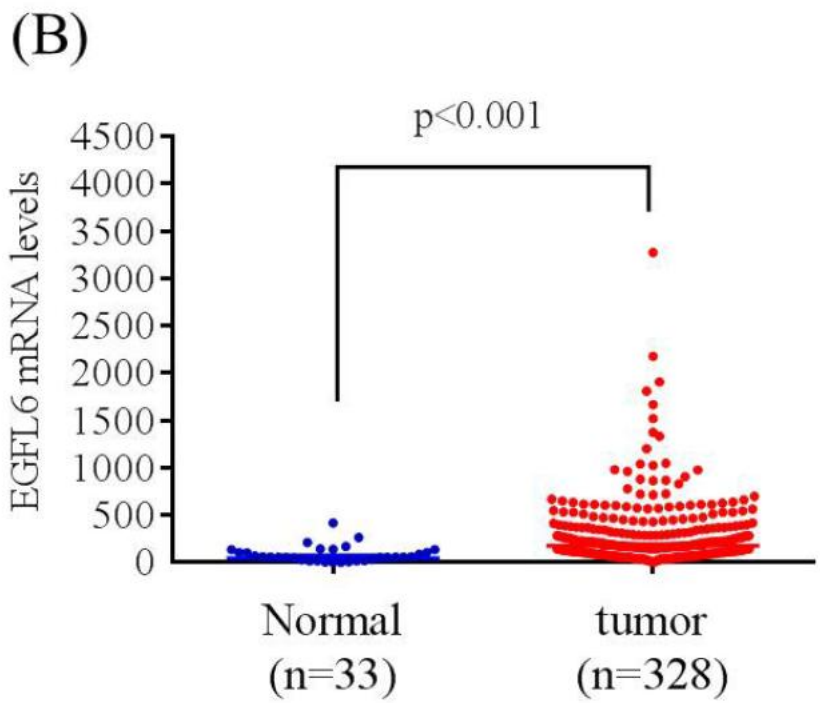

Figure 1B. EGFL6 mRNA expressions were compared according to normal tissue and OSCC patients' tissue from TCGA database.

Figure 1C

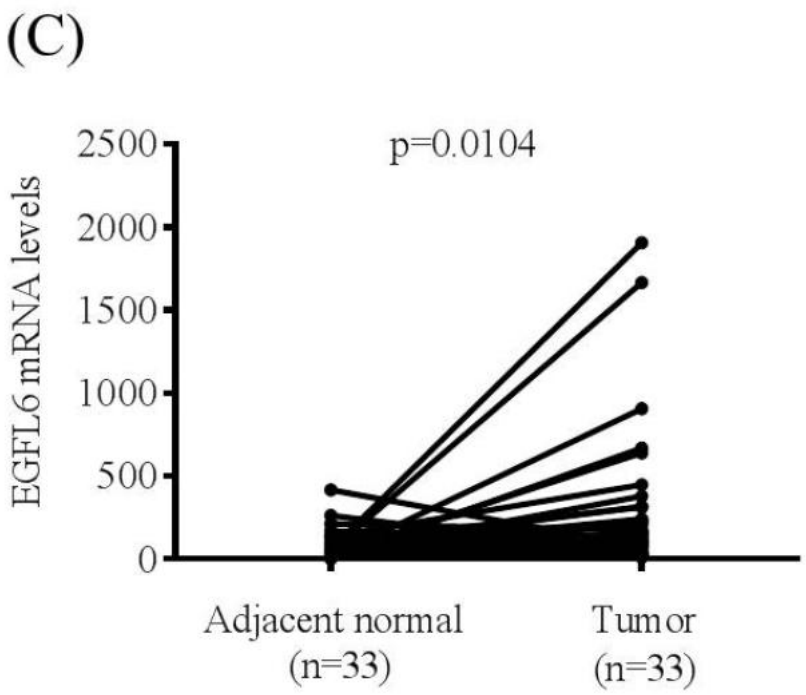

Figure 1C. Relative expression of EGFL6 in 33 pairs of oral squamous cell carcinoma tumor tissues and their corresponding adjacent non-cancerous tissues.

Figure 2

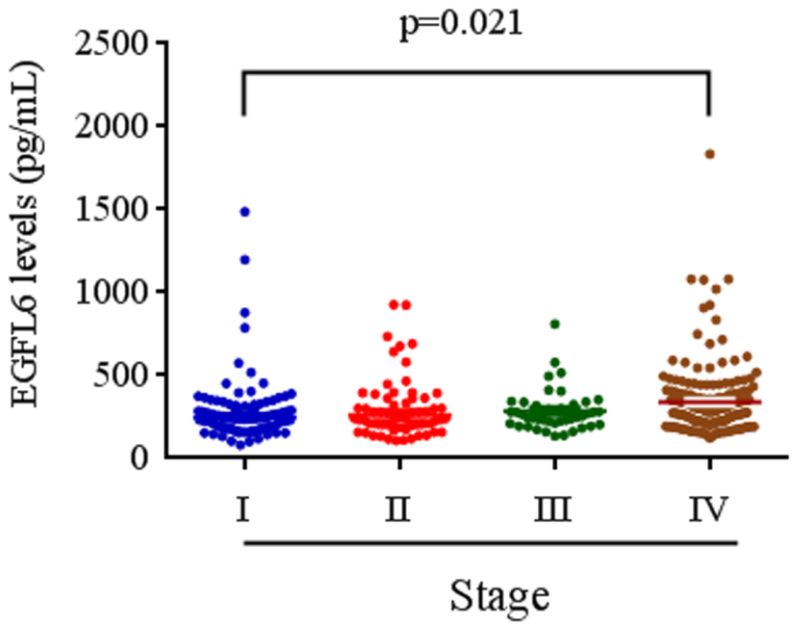

Figure 2. EGFL6 levels were compared according to stage. The levels of EGFL6 were significantly higher in the patients with stage IV (332.83 pg/mL) compared to those with an early stage (stage I: 274.22 pg/mL).

Figure 3

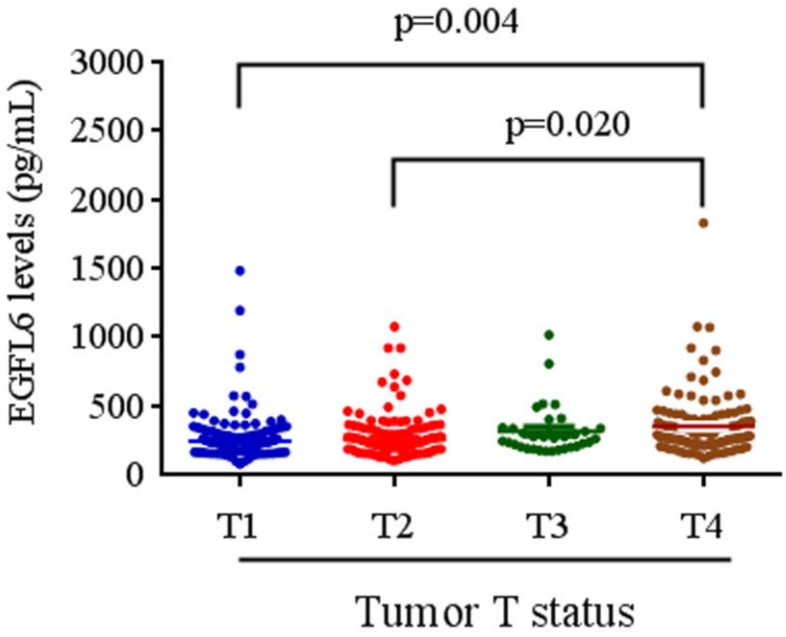

Figure 3. EGFL6 levels were compared according to tumor T status. The levels of EGFL6 were significantly higher in the patients with advanced tumor T status (T4: 347.73 pg/mL) compared to those with early T status (T1: 273.67 pg/mL and T2: 286.64 pg/mL; p=0.004 and p=0.020).

科技部補助專題研究計畫出席國際學術會議心得報告

日期：106 年 7 月 1 日

計畫編號	MOST 105-2320-B-040-001-MY2		
計畫名稱	新穎基因第六型表皮生長因子類蛋白在口腔癌致癌過程的表現及其調控癌症轉移之機制探討		
出國人員姓名	周英二	服務機構及職稱	中山醫學大學醫學系法醫學科 助理教授
會議時間	2017 年 6 月 24 日 至 2017 年 6 月 27 日	會議地點	Florence, Italy
會議名稱	(中文) 2017 年歐洲癌症研究協會-美國癌症研究協會-義大利癌症協會特別會議 (英文) EACR-AACR-SIC Special Conference 2017		
發表題目	(中文) WNT1 所誘導之訊號路徑蛋白 1 基因微型核糖核酸結合位置的基因變異對於口腔鱗狀細胞癌易感性的影響 (英文) Effect of genetic variation in microRNA binding site in WNT1-inducible signaling pathway protein 1 gene on oral squamous cell carcinoma susceptibility		

一、參加會議經過

6/23 抵達佛羅倫斯之後，隔天即前往大會地點 Firenze Fiera 報到(Fig.1)並領取本次大會議程及摘要手冊。本次大會安排我的研究成果海報張貼日期是在 6/26，因此在前兩天能夠有充裕的時間在現場聆聽許多不同國家學者的會議報告與大會專題演講，或是參觀口腔癌亦或是其他癌症研究相關領域的成果發表。6/26 當天在成果海報發表處講解研究內容(Fig.2)，並於 6/27 結束本次 EACR-AACR-SIC Special Conference 2017: The Challenges of Optimizing Immuno- and Targeted Therapies: From Cancer Biology to the Clinic 大會議程。

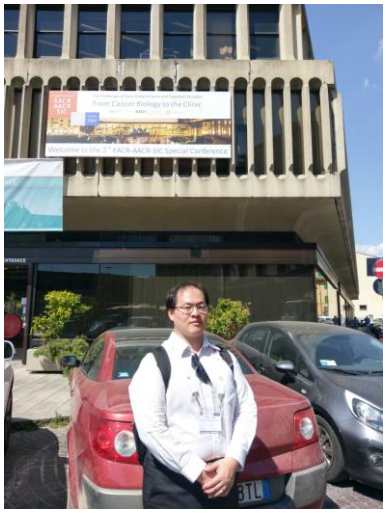

Fig.1 大會地點

Fig.2 海報展示

二、與會心得

本次參加在義大利佛羅倫斯舉辦的 2017 年歐洲癌症研究協會-美國癌症研究協會-義大利癌症協會特別會議，與許多世界各國的優秀學者接觸交流之後，對於目前在從事的口腔癌相關研究得到了不少經驗和發想。對於自己海報研究成果的展示交流與外國學者做經驗分享時，比較能掌握應答的訣竅，漸漸不會那麼緊張了。不過在與會的過程中尤其是聽到大會演講時，對照一些台上學者在演說講解發表的實驗結果、所探討的訊號路徑，偶爾發現與自己目前有在操作接觸的相關實驗有關的議題，比較對照思考之後，會很想督促激勵自己再投稿發表到更好的期刊，也會很想盡快掌握明明是同樣在探討同樣類似的實驗，具體到底是存在有甚麼差異造成發表的文章程度在投稿的期刊有天壤之別！魔鬼藏在細節裡。期許自己在不斷參加學術研討會的歷程中，莫忘一個學者教授該有的自我期許高度、積極度與企圖心，早日讓自己的學術專長有所突破，有朝一日帶領我們國家的學術研究再創高峰!

除了海報發表報告之外，整個會場的布置相當富有藝術氣息，設計規劃讓與會者非常能夠靜下心來沉浸在學術的氛圍中，不禁讚嘆佛羅倫斯不愧是文藝復興的發源地！在會場中聽到的大會口頭報告演講或是海報展示靜態空間的安排都讓自己對於義大利這個國家有著很清新的認識與感受。藉由參加這樣國際級的會議也更期許激勵自己在這樣的場合能夠有更卓越的成果發表，得以進一步與外國學者做交流分享。參加這次 EACR-AACR-SIC Special Conference 2017 會議著實獲益良多。

三、發表論文全文或摘要

Abstract

Introduction: Oral squamous cell carcinoma (OSCC), which is the most common head and neck cancer, accounts for 1%–2% of all human malignancies and is characterized by poor prognosis and reduced survival rates. WNT1-inducible signaling pathway protein 1 (WISP1), a cysteine-rich protein belonging to the Cyr61, CTGF, Nov (CCN) family of matricellular proteins, has many developmental functions and may be involved in carcinogenesis. This study investigated WISP1 single-nucleotide polymorphisms (SNPs) to elucidate OSCC susceptibility and clinicopathologic characteristics.

Material and method: We genotyped 4 single nucleotide polymorphisms of WISP1 rs16893344, rs2977530, rs2977537, and rs2929970 from 900 OSCC patients and 1200 cancer-free controls. The association between WISP1 expression and WISP1 genetic polymorphism was analysed in the

Encyclopedia of DNA Elements (ENCODE) data from the NCBI gene database and confirmed by quantitative real-time PCR.

Results and discussion: The WISP1 rs2929970 polymorphism carriers with at least one G allele were susceptible to OSCC. Moreover, compared with wild-type carriers, we observed that among 100 nonsmoker OSCC patients, those carrying WISP1 rs2929970 AG + GG genotypes had later stage OSCC (stages III and IV) and a larger tumor size. Because smoking is a well-known risk factor for OSCC, this result in nonsmoker OSCC patients implicated the pivotal role of the WISP1 SNP of rs2929970 in cancer progression and WISP1 regulation. In addition, OSCC patients who were betel quid chewers and carried WISP1 rs16893344 (CT + TT) variants had a low risk of lymph node metastasis. Finally, bioinformatics analysis was used to characterize the functional relevance of these variants for the microRNA-99a binding site and transcriptional regulation by the WISP1 3′-UTR and promoter regions.

Conclusion:

The WISP1 SNP of rs2929970 is associated with OSCC susceptibility, and rs2929970 A/G polymorphisms may be correlated with a worse prognosis of OSCC, such as later stage OSCC or larger tumor size. WISP1 rs2929970 may serve as a marker or a therapeutic target in OSCC.

四、建議

首先感謝科技部給予補助專題研究計畫出席國際會議，因此得以來到義大利佛羅倫斯與各國癌症研究領域的專家學者交流切磋，整趟學會行程下來得到許多收穫！期待國內也能夠多舉辦類似的大型國際會議廣邀知名學者及相關研究領域權威來演講交流，除了促成學術研究專業的往來交流之餘，對於提升我們國家的研究水準與國家形象將有相當大的幫助。而專家學者學術人才彼此的經驗和成果分享也可以激盪淬鍊出更具實用性與前瞻性的意見和想法，提升與會者的眼界並且激勵自己。因此深切感謝之餘，建議多補助計畫主持人出國參加會議，除了在學術研究上可以帶回新的經驗和想法，對於我們國家的年輕學者提升學術高度、掌握各國其專業領域的研究近況以及觀念的革新上將深有助益。

五、攜回資料名稱及內容

會議議程手冊
會議摘要手冊

六、其他

無

105年度專題研究計畫成果彙整表

計畫主持人：周英二	**計畫編號：**105-2320-B-040-001-MY2
計畫名稱：新穎基因第六型表皮生長因子類蛋白在口腔癌致癌過程的表現及其調控癌症轉移之機制探討	

成果項目					量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文			0	篇	
		研討會論文			0		
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		
	技術移轉	件數			0	件	
		收入			0	千元	
國外	學術性論文	期刊論文			1	篇	International journal of medical sciences, 2017; 14: 419 - 424.
		研討會論文			2		Effects of WW domain-containing oxidoreductase(WWOX) gene polymorphisms in the Kozaksequence on the risk and progression of oral cancer, 24th Biennial Congress of the European Association for Cancer Research (EACR24), Manchester UK, 9-12 July 2016. Effect of genetic variation in microRNA binding site in WNT1-inducible signaling pathway protein 1 gene on oral squamous cell carcinoma susceptibility, EACR-AACR-SIC Special Conference 2017: The Challenges of Optimising Immuno and Targeted Therapies: From Cancer Biology to the Clinic, Florence

						Italy, 24 – 27 June 2017.
		專書			0	本
		專書論文			0	章
		技術報告			0	篇
		其他			0	篇
	智慧財產權及成果	專利權	發明專利	申請中	0	件
				已獲得	0	
			新型/設計專利		0	
		商標權			0	
		營業秘密			0	
		積體電路電路布局權			0	
		著作權			0	
		品種權			0	
		其他			0	
	技術移轉	件數			0	件
		收入			0	千元
參與計畫人力	本國籍	大專生			0	人次
		碩士生			0	
		博士生			0	
		博士後研究員			0	
		專任助理			1	專任助理 林佳潔
	非本國籍	大專生			0	
		碩士生			0	
		博士生			0	
		博士後研究員			0	
		專任助理			0	
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。）						

科技部補助專題研究計畫成果自評表

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（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）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（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊）
   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200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）
   EGFL6 (epidermal growth factor-like domain multiple-6)又稱為MAEG，過去的研究已鑑識出其位於人類染色體圖譜Xp22的位置並且在胎兒組織與早期發育中大量表現。然而EGFL6的表現與口腔癌之間的關聯性仍然尚未明瞭。本研究針對392位口腔鱗狀上皮癌(oral squamous cell carcinoma, OSCC)的患者以酵素免疫分析法（Enzyme-Linked ImmunoSorbent Assay, ELISA）分析患者血漿中的EGFL6表現量，發現當患者具有較大的腫瘤體積（T status, $p = 0.002$），遠端轉移（distant metastasis, $p = 0.001$），還有較高的TNM分期（$p = 0.033$）時，血漿中的EGFL6具有顯著較高的表現量。因此，EGFL6除了參與OSCC的致癌物作用(carcinogenesis)之外，在臨床應用上也或許可以作為OSCC患者的腫瘤標記(biomarker)。

4. 主要發現
   本研究具有政策應用參考價值：■否　□是，建議提供機關
   （勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
   本研究具影響公共利益之重大發現：□否　□是
   說明：（以150字為限）