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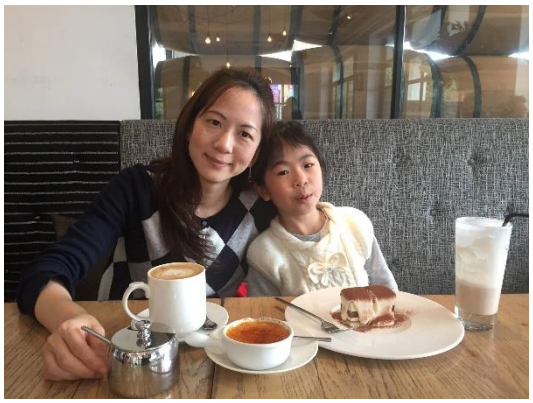

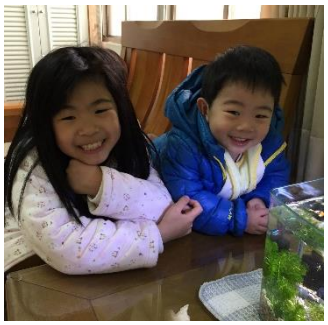

學經歷

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博士，國防醫學院 生命科學研究所
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碩士，陽明大學 公共衛生研究所
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學士，長庚大學 醫事技術學系
B.S., Dept. of Medical Biotechnology and Laboratory Science, Chang Gung University, Taiwan.

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Assistant Professor, Dept. of Microbiology & Immunology, Chang Gung University, Taiwan

2014/3~2016/7

Assistant Research Fellow, Molecular Medicine Research Center, Chang Gung University, Taiwan.

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Postdoctoral Fellow, Immunology Research Center, National Health Research Institutes, Taiwan.

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Postdoctoral Fellow, Institute of Molecular Biology, Academia Sinica, Taiwan.

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Research Assistant, Institute of Molecular Biology, Academia Sinica, Taiwan.

研究方向

1. 感染性肺炎的免疫調節因子鑑定與功能性探討

肺炎(pneumonia)是指肺部實質出現發炎的現象，其致病原以感染細菌或病毒為主，偶有其他微生物的感染而引起。肺炎常見的症狀有咳嗽、胸痛、發熱與呼吸困難，約有百分之四十的肺炎病人會合併出現肋膜腔積液，肋膜腔積液的產生會大幅增加肺炎病人的死亡率，抗生素治療或搭配胸管引流是目前臨床上治療的選擇。我們利用蛋白質體學技術(Proteomics)，系統性的建立肺炎病人肋膜腔積液的蛋白質體資料庫，並從其中鑑定出多個參與免疫調節機制的新穎蛋白標誌(immune-related biomarker)，我們評估這些新穎的蛋白標誌在臨床應用於肺炎病人分期、治療與預後的成效，更進一步探討這些免疫調節因子在肺炎中扮演的生物學角色與機轉。我們也利用代謝體學技術(Metabolomics)，分析肺炎病人肋膜腔積液的代謝分子組成，期望鑑定出與疾病相關的代謝分子，並探討其生物功能。同時，肺炎病人肋膜腔積液中也存在著大量的免疫細胞，其中以嗜中性球為主，我們以基因體學技術(Genomics/Next-generation sequencing)，分析免疫細胞的轉錄體變化，期望了解免疫細胞在於疾病進展的機轉與角色。我們期望以感染性肺炎為模式，串連高通量實驗的數據，建立免疫體學的應用。

2. 口腔癌的微生物菌相分析與癌化功能性探討:

口腔癌是指發生在口腔各個部位的惡性腫瘤，其中大約有九成都是屬於鱗狀細胞癌，好發於 45 歲以上的男性，但近年來口腔癌好發年紀有下降趨勢。嚼食檳榔、吸菸、喝酒、蛀牙與不良的口腔衛生習慣等等，都是可能的危險子。治療

方式是以外科手術和放射線治療為主，有些病人會搭配抗癌藥物的化學治療。口腔癌早期個案治療後，有七成以上的人其五年存活率很好，所以早期發現與治療會有相當好的成效。我們實驗室關注於口腔癌的癌化機轉研究，我們建立口腔癌的癌症動物模式以及人類腫瘤細胞異體移植動物模式，以研究口腔癌病患的病理及基因多樣性，並分析腫瘤細胞對藥物的敏感性以及免疫相關訊號路徑的調控。此外，我們也分析病原菌和口腔癌的相關性，利用次世代定序平台，建立口腔癌病人的口水與癌組織的菌相圖譜，進一步探究病原菌在口腔癌之癌化機轉的角色。**我們非常歡迎對基因體學，腫瘤生物學，感染免疫學有興趣的大學部專題生與碩博班研究生加入實驗室，進行專題研究與碩博士論文研究。**

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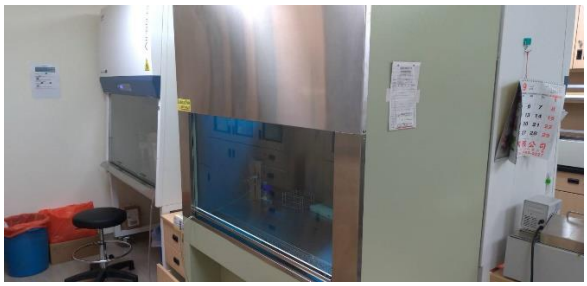

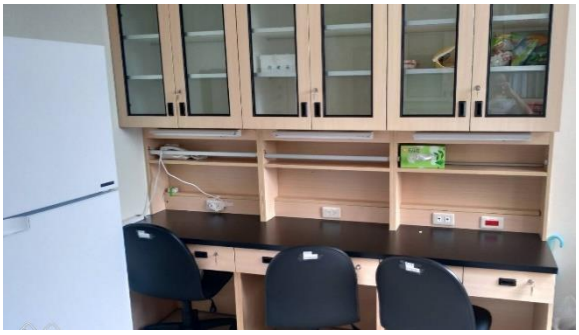

近期著作

frontiers in Microbiology

ORIGINAL RESEARCH
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Oral Microbiota Community Dynamics Associated With Oral Squamous Cell Carcinoma Staging

Chia-Yu Yang[1,2,3,4], Yuan-Ming Yeh[3,5], Hai-Ying Yu[6], Chia-Yin Chin[3], Chia-Wei Hsu[3], Hsuan Liu[2,3,4,7], Po-Jung Huang[2,3,5,8], Song-Nian Hu[6], Chun-Ta Liao[9], Kai-Ping Chang[3,9] and Yu-Liang Chang[10]**

Oral squamous cell carcinoma (OSCC) is a highly aggressive cancer and the fourth leading malignancy among males in Taiwan. Some pathogenic bacteria are associated with periodontitis and oral cancer. However, the comprehensive profile of the oral microbiome during the cancer's progression from the early stage to the late stage is still unclear. We profiled the oral microbiota and identified bacteria biomarkers associated with OSCC. The microbiota of an oral rinse from 51 healthy individuals and 197 OSCC patients at different stages were investigated using 16S rRNA V3V4 amplicon sequencing, followed by bioinformatics and statistical analyses. The oral microbiota communities from stage 4 patients showed significantly higher complexity than those from healthy controls. The populations also dynamically changed with the cancer's progression from stage 1 to stage 4. The predominant phyla in the oral samples showed variation in the relative abundance of *Fusobacteria, Bacteroidetes*, and *Actinobacteria*. The abundance of *Fusobacteria* increased significantly with the progression of oral cancer from the healthy controls (2.98%) to OSCC stage 1 (4.35%) through stage 4 (7.92%). At the genus level, the abundance of *Fusobacterium* increased, while the number of *Streptococcus, Haemophilus, Porphyromonas*, and *Actinomyces* decreased with cancer progression. *Fusobacterium periodonticum, Parvimonas micra, Streptococcus constellatus, Haemophilus influenza*, and *Filifactor alocis* were associated with OSCC, and they progressively increased in abundance from stage 1 to stage 4. The abundances of *Streptococcus mitis, Haemophilus parainfluenzae*, and *Porphyromonas pasteri* were inversely associated with OSCC progression. We selected a bacterial marker panel of three bacteria (upregulated *F. periodonticum*, down-regulated *S. mitis*, and *P. pasteri*), which had an AUC of 0.956 (95% CI = 0.925-0.986) in discriminating OSCC stage 4 from the healthy controls. Furthermore, the functional prediction of oral bacterial communities showed that genes involved in carbohydrate-related metabolism, such as methane metabolism, and energy-metabolism-related parameters, such as oxidative phosphorylation and carbon fixation in photosynthetic organisms, were enriched in late-stage OSCC, while those responsible for amino acid metabolism, such as folate biosynthesis and valine, leucine, and isoleucine biosynthesis, were significantly associated with the healthy controls. In conclusion, our results provided evidence of oral bacteria community changes during oral cancer progression and suggested the

possibility of using bacteria as OSCC diagnostic markers.

SCIENTIFIC REPORTS

OPEN

Proteome profiling reveals novel biomarkers to identify complicated parapneumonic effusions

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Kuo-An Wu[1,2], Chih-Ching Wu[3,4,5], Chi-De Chen[5], Chi-Ming Chu[6], Li-Jane Shih[7,8], Yu-Ching Liu[3], Chih-Liang Wang[9], Hsi-Hsien Lin[10,11] & Chia-Yu Yang[5,10,12]

Patients with pneumonia and parapneumonic effusion (PPE) have elevated mortality and a poor prognosis. The aim of this study was to discover novel biomarkers to help distinguish between uncomplicated PPE (UPPE) and complicated PPE (CPPE). Using an iTRAQ-based quantitative proteomics, we identified 766 proteins in pleural effusions from PPE patients. In total, 45 of these proteins were quantified as upregulated proteins in CPPE. Four novel upregulated candidates (BPI, NGAL, AZU1, and calprotectin) were selected and further verified using enzyme-linked immunosorbent assays (ELISAs) on 220 patients with pleural effusions due to different causes. The pleural fluid levels of BPI, NGAL, AZU1, and calprotectin were significantly elevated in patients with CPPE. Among these four biomarkers, BPI had the best diagnostic value for CPPE, with an AUC value of 0.966, a sensitivity of 97%, and a specificity of 91.4%. A logistic regression analysis demonstrated a strong association between BPI levels > 10 ng/ml and CPPE (odds ratio = 341.3). Furthermore, the combination of pleural fluid BPI levels with LDH levels improved the sensitivity and specificity to 100% and 91.4%, respectively. Thus, our findings provided a comprehensive effusion proteome data set for PPE biomarker discovery and revealed novel biomarkers for the diagnosis of CPPE.

Induction of DUSP14 ubiquitination by PRMT5-mediated arginine methylation.

Yang CY, Chiu LL, Chang CC, Chuang HC, Tan TH.
FASEB J. 2018 Jun 19:fj201800244RR. doi: 10.1096/fj.201800244RR. [Epub ahead of print]

Dual-specificity phosphatase (DUSP)14 (also known as MAP-kinase phosphatase 6) inhibits T-cell receptor (TCR) signaling and T-cell-mediated immune responses by inactivation of the TGF-β activated kinase 1 binding protein (TAB1)-TGF-β activated kinase 1 (TAK1) complex and ERK. DUSP14 phosphatase activity is induced by the E3 ligase TNF receptor associated factor (TRAF)2-mediated Lys63-linked ubiquitination. Here we report an interaction between DUSP14 and protein arginine methyltransferase (PRMT)5 by proximity ligation assay; similarly, DUSP14 directly interacted with TAB1 but not TAK1. DUSP14 is methylated by PRMT5 at arginine 17, 38, and 45 residues. The DUSP14

triple-methylation mutant was impaired in PRMT5-mediated arginine methylation, TRAF2-mediated lysine ubiquitination, and DUSP14 phosphatase activity. Consistently, DUSP14 methylation, TRAF2 binding, and DUSP14 ubiquitination were attenuated by PRMT5 short hairpin RNA knockdown. Furthermore, DUSP14 was inducibly interacted with PRMT5 and was methylated during TCR signaling in T cells. Together, these findings reveal a novel regulatory mechanism of DUSP14 by which PRMT5-mediated arginine methylation may sequentially stimulate TRAF2-mediated DUSP14 ubiquitination and phosphatase activity, leading to inhibition of TCR signaling.

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TRAF2-mediated Lys63-linked ubiquitination of DUSP14/MKP6 is essential for its phosphatase activity

Chia-Yu Yang [a,1], Li-Li Chiu [b,1], Tse-Hua Tan [c,d,e,*]

Dual-specificity phosphatase 14 (DUSP14, also known as MKP6) is a MAP kinase phosphatase that dephosphorylates JNK, ERK, and p38 in vitro. We recently reported that DUSP14 negatively regulates T-cell activation and immune responses by interfering activation of TAB1-TAK1 complex. However, the molecular mechanism that regulates the phosphatase activity of DUSP14 remains unclear. Here, we report the post-translational modification of DUSP14 by ubiquitination. Mass spectrometry and mutational analyses identified that DUSP14 was Lys63-linked ubiquitinated at lysine 103 residue. Furthermore, DUSP14 inducibly interacted with the E3 ligase TRAF2 during T-cell receptor (TCR) signaling; TRAF2 shRNA knockdown reduced the DUSP14 ubiquitination. We also show that ubiquitination of DUSP14 was required for its phosphatase activity during TCR signaling. Together, these findings reveal a novel mechanism by which TRAF2 mediates Lys63-linked ubiquitination of DUSP14, leading to DUSP14 activation in T cells.

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