

優秀論文獎_基礎

時間：114年11月22日(星期六)09:10-10:10

地點：台中林酒店 3F 國際廳

摘要：

座長/Moderator	國泰醫院 林世昌醫師
09:10-09:22	<p>Single-Cell Transcriptomics Reveals Progressive Immune Dysregulation from Healthy State to Preclinical and Established Systemic Lupus Erythematosus <u>Wei-Ting Hung</u>^{1,2,3}, Ting-Shuan Wu⁴, Yi-Ming Chen^{1,5,6}</p> <p>¹Division of Allergy, Immunology, and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan ²Department of Medical Education, Taichung Veterans General Hospital, Taichung, Taiwan ³Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan ⁴Department of Biomedical Sciences, Chung Shan Medical University, Taichung, Taiwan ⁵Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan ⁶College of Medicine, National Chung Hsing University, Taiwan</p> <p>運用單細胞轉錄體技術解析健康至前期與確診系統性紅斑狼瘡的免疫失衡演進 洪維廷, 吳亭萱, 陳一銘 台中榮總內科部過敏免疫風濕科、台中榮總教學部、台中榮總醫學研究部、中山醫學大學生物醫學科學學系、中興大學醫學院</p>
09:22-09:25	Q & A
09:25-09:37	<p>3-chymotrypsin-like protease from SARS-CoV-2 induces alveolar hemorrhage and lupus nephritis by enhancing apoptosis and autophagy formation in systemic lupus erythematosus patients and experimental mouse model Chrong-Reen Wang^{1,2,3}, Yi-Cheng Chen¹, Yu-Tung Hsieh², Chia-Tse Weng¹, Wei-Chieh Lin¹, Yi-Ting Yen⁴, Hung-Wen Tsai⁵, Ping Lin³, Yu-Chi Chou⁶</p> <p>¹Department of Internal Medicine, ²Institute of Basic Medical Sciences, ³Department of Microbiology and Immunology, ⁴Department of Pathology, ⁵Department of Surgery, College of Medicine, National Cheng Kung University, ⁶Biomedical Translation Research Center, Academia Sinica</p> <p>SARS-冠狀病毒 2 之 3-糜蛋白酶樣蛋白酶經由促進細胞凋亡及自體吞噬形成來引發全身性紅斑狼瘡患者與實驗小鼠模型的狼瘡腎炎與肺泡出血 <u>王崇任</u>^{1,2,3}、<u>陳怡成</u>¹、<u>謝雨彤</u>²、<u>翁嘉澤</u>¹、<u>林偉傑</u>¹、<u>顏亦廷</u>⁴、<u>蔡弘文</u>⁵、<u>凌斌</u>³、<u>周祐吉</u>⁶</p> <p>¹成大醫學院附設醫院內科部、²成大醫學院基醫所、³成大醫學院微免所、⁴成大醫學院附設醫院病理部、⁵成大醫學院附設醫院外科部、⁶中研院生醫轉譯研究中心</p>
09:37-09:40	Q & A

09:40-09:52	<p>TLR7-Mediated Regulation of Signaling and Phenotypic Changes by R837 in Pulmonary Artery Smooth Muscle Cells TLR7介導R837调控肺動脈平滑肌細胞訊息傳遞與表型變化</p> <p>Xiao-Fan Huang¹, Huang Kun-Lun^{2,3}, Chun-Hsien Wu⁴, Yi-Lin Chiu⁵, Fu-Chiang Yeh¹ 黃曉凡¹, 黃坤崙^{2,3}, 吳俊賢⁴, 邱奕霖⁵, 葉富強¹</p> <p>¹ Division of Rheumatology, Immunology and Allergy, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan ² Institute of Aerospace and Undersea Medicine, National Defense Medical Center, Taipei, Taiwan. ³ Division of Pulmonary and Critical Care, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. ⁴ Division of Cardiology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. ⁵ Department of Biochemistry, National Defense Medical Center, Taipei, Taiwan.</p> <p>1 國防醫學院三軍總醫院風濕免疫科 2 國防醫學院航太及海底醫學研究所 3 國防醫學院三軍總醫院內科部呼吸與重症醫學科 4 國防醫學院三軍總醫院內科部心臟內科 5 國防醫學院生物化學研究所</p>
09:52-09:55	Q & A
09:55-10:07	<p>The anti-inflammatory effect of Atracylodin in the mouse model of autoimmune hepatitis Atracylodin 於自體免疫性肝炎小鼠模型之抗發炎效果</p> <p>楊登和^{1,2,3,4}、林季千⁴</p> <p>¹ Division of Rheumatology/Immunology/Allergy, Department of Internal Medicine, Taichung Armed-Forces General Hospital, Taichung, Taiwan ² Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung, Taiwan ³ Division of Rheumatology/Immunology/Allergy, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan ⁴ Institute of Biomedical Science, National Chung-Hsing University, Taichung, Taiwan</p>
10:07-10:10	Q & A

Single-Cell Transcriptomics Reveals Progressive Immune Dysregulation from Healthy State to Preclinical and Established Systemic Lupus Erythematosus

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運用單細胞轉錄體技術解析健康至前期與確診系統性紅斑狼瘡的免疫失衡演進洪維廷, 吳亭萱, 陳一銘

台中榮總內科部過敏免疫風濕科、台中榮總教學部、台中榮總醫學研究部、中山醫學大學生物醫學科學學系、中興大學醫學院

Background: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by immune dysregulation and progressive tissue involvement. Early identification of immune alterations prior to clinical onset remains a major challenge. This study investigates the immunological transitions from healthy individuals to preclinical SLE (pre-SLE) and established SLE using single-cell transcriptomic profiling.

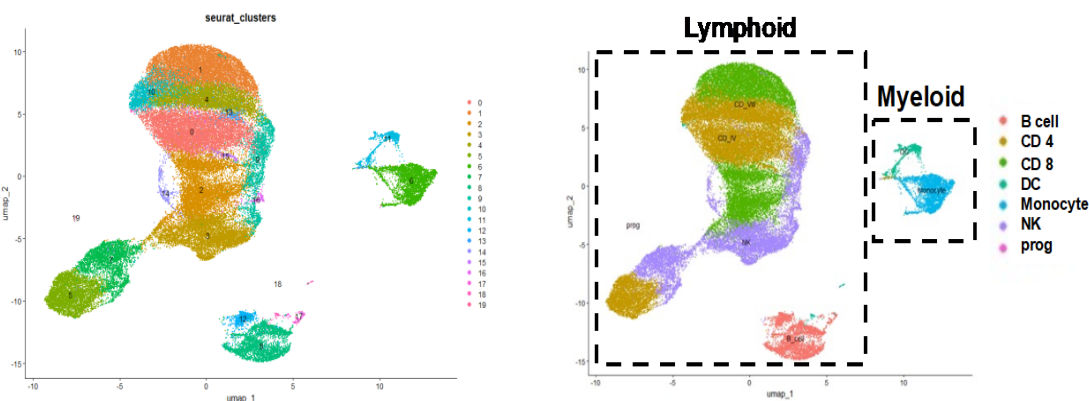
Materials and Methods: Peripheral blood mononuclear cells (PBMCs) were collected from 10 healthy controls, 23 individuals with high genetic susceptibility for SLE (top 5% of SLE polygenic risk score [PRS], but no clinical diagnosis), and 12 patients with clinically confirmed SLE. Single-cell RNA sequencing (scRNA-seq) was conducted using the BD Rhapsody platform. Downstream data analysis was performed using Seurat and complementary bioinformatics tools to cluster cells, identify differentially expressed genes (DEGs), and perform pathway enrichment analysis.

Results: Unsupervised clustering and UMAP projection annotated five major immune cell types—B cells, CD4⁺ T cells, CD8⁺ T cells, monocytes, and NK cells—which were further grouped into lymphoid and myeloid lineages. The myeloid-to-lymphoid (M/L) ratio showed a progressive increase from healthy controls to pre-SLE and SLE groups, indicating enhanced myeloid cell prevalence along the disease trajectory. Volcano plot analysis of DEGs revealed that pre-SLE individuals already exhibited significant transcriptional shifts, notably upregulation of immune activation markers such as IFI44L and XAF1. These molecular perturbations preceded clinical disease onset and were further accentuated in SLE patients.

Conclusion: Our single-cell analysis reveals progressive immune dysregulation from genetically susceptible individuals to those with overt SLE. The distinct gene expression profiles and altered immune compositions suggest that molecular signatures such as IFI44L and XAF1 may serve as early biomarkers and potential therapeutic targets. These findings enhance our understanding of lupus pathogenesis and support the development of precision strategies for early intervention.

Figure

(A)



(B)

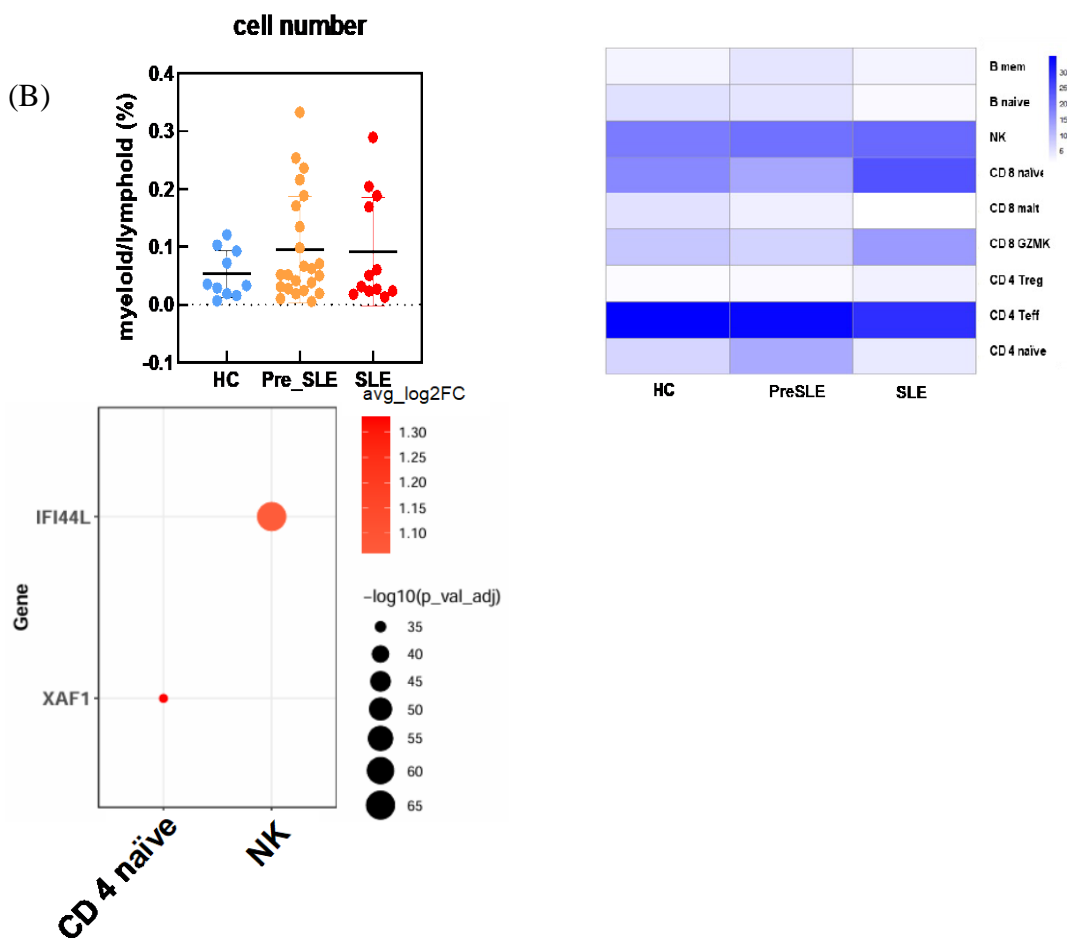


Figure Single-cell RNA sequencing reveals progressive immune alterations across healthy controls, preclinical SLE (pre-SLE), and SLE patients.

(A) UMAP visualization of peripheral blood mononuclear cells (PBMCs) from all participants clustered using the Seurat pipeline, with clusters annotated into 19 transcriptionally distinct subpopulations. Annotation of major immune cell lineages into B cells, CD4⁺ T cells, CD8⁺ T cells, dendritic cells (DCs), monocytes, natural killer (NK) cells, and progenitor cells. Quantification of the myeloid-to-lymphoid ratio in healthy controls (blue), pre-SLE (orange), and SLE patients (red), indicating a progressive shift toward myeloid predominance. Heatmap showing relative abundance of lymphoid subpopulations across groups, including memory and naïve B cells, NK cells, CD8⁺ naïve and cytotoxic subsets (MAIT, GZMK), and CD4⁺ subtypes (naïve, Treg, Teff). (B) Dot plot depicting differentially expressed genes IFI44L and XAF1 between healthy controls and pre-SLE individuals in selected lymphoid subsets. Dot size indicates statistical significance ($-\log_{10}$ adjusted p-value) and color denotes log₂ fold change.

3-chymotrypsin-like protease from SARS-CoV-2 induces alveolar hemorrhage and lupus nephritis by enhancing apoptosis and autophagy formation in systemic lupus erythematosus patients and experimental mouse model

Chrong-Reen Wang^{1,2,3}, Yi-Cheng Chen¹, Yu-Tung Hsieh², Chia-Tse Weng¹, Wei-Chieh Lin¹, Yi-Ting Yen⁴, Hung-Wen Tsai⁵, Ping Lin³, Yu-Chi Chou⁶

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SARS-冠狀病毒2之3-糜蛋白酶樣蛋白酶經由促進細胞凋亡及自體吞噬形成來引發全身性紅斑狼瘡患者與實驗小鼠模型的狼瘡腎炎與肺泡出血

王崇任^{1,2,3}、陳怡成¹、謝雨彤²、翁嘉澤¹、林偉傑¹、顏亦廷⁴、蔡弘文⁵、凌斌³、周祐吉⁶

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Background: SLE pathogenesis involves cell death to release autoantigens, forming immune complexes with visceral deposition to develop alveolar hemorrhage (AH) and lupus nephritis (LN), *etc.* SARS-CoV-2 infection can induce SLE flares. Despite elucidated cell death mechanisms by SARS-CoV-2-associated RNAs/proteins, the role of 3-chymotrypsin-like protease (3CLpro) remain unexplored.

Methods: Peripheral blood (PB), urine and lung/renal tissues were from SLE with post-COVID-19 flares. Lentivirus (LV)-3CLpro, LV-miR-146a, CRISPR-Cas6/Csm-SNHG16, sh-TRAF6 and sh-miR-146a were generated. mTOR protein were mixed with 3CLpro. LV-3CLpro-transfected alveolar cells were analyzed for cell death and expression of apoptosis/autophagy inhibitors and NLRP12 (NF- κ B repressor). Pristane-induced AH mice received LV-3CLpro or LV-3CLpro/sh-TRAF6 intra-pulmonary delivery. Pristane-induced LN mice were under LV-3CLpro infusion.

Results: There were lower miR-146a and higher TRAF6 (miR-146a-target molecule), SNHG16 (miR-146a-endogenous RNA), cell death-related p53/LC3 and IL-6 levels in PB mononuclear cells and AH lung tissues from SLE with post-COVID-19 flares. mTOR was cleaved by 3CLpro. LV-3CLpro-transfected cells had lower miR-146a, apoptosis/autophagy inhibitors and NLRP12 expression and higher TRAF6, SNHG16, p53/LC3 and IL-6 levels with increased apoptosis/autophagy formation. LV-3CLpro infusion enhanced AH by increasing intra-pulmonary cell death through reducing apoptosis/autophagy inhibitors and NLRP12 expression, while AH was suppressed by LV-3CLpro/sh-TRAF6 infusion. There were lower TRAF6 and SNHG16 and higher miR-146a and IFN- γ levels in urine sediment cells and LN renal tissues from SLE with post-COVID-19 flares. LV-3CLpro delivery aggravated LN with increased proteinuria, IgG anti-RNP and glomerular proliferation/IgG deposition.

Conclusions: Our results demonstrate the role of cell death by 3CLpro-mediated cleavage of apoptosis/autophagy inhibitors and NLRP12 in post-COVID-19 SLE flares.

TLR7-Mediated Regulation of Signaling and Phenotypic Changes by R837 in Pulmonary Artery Smooth Muscle Cells

TLR7介導R837调控肺動脈平滑肌細胞訊息傳遞與表型變化

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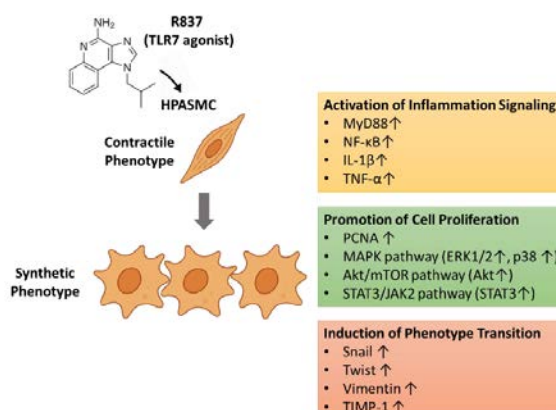
Abstract

Background: Our previous study has demonstrated that Toll-like receptor 7 (TLR7) activation of plasmacytoid dendritic cells (pDCs) promotes autoimmune disease-associated pulmonary arterial hypertension (PAH) in rat. However, the direct effects of TLR7 activation on pulmonary vascular cells remain unclear. In this study, we investigated the impact of R837, a selective TLR7 agonist, on human pulmonary artery smooth muscle cells (HPASMCs).

Methods: HPASMCs were treated with R837, followed by MTT assay, flow cytometry, and western blot analysis to investigate the associated signaling pathways.

Results: Our preliminary data showed that R837 increased the viability of HPASMCs. To further explore the underlying mechanisms, we examined markers of cell proliferation and found that PCNA expression was upregulated, suggesting that R837 promotes HPASMC proliferation by activating the cell cycle. Additionally, we observed increased expression of signaling proteins associated with the Akt, STAT3, and MAPK (ERK1/2 and p38) pathways. To assess whether R837 induces phenotypic switching in HPASMCs from a contractile to a synthetic state, which is evident in human PAH, we analyzed the expression of relevant markers. The results revealed upregulation of Snail, Twist1, TIMP-1, and vimentin, indicating a transition toward a synthetic phenotype. We further explored the involvement of TLR7 signaling, a pathway well characterized in immune cells. While TLR7 expression itself was not significantly altered, the expression of MyD88, NF- κ B, TNF- α , and IL-1 β was markedly increased, supporting activation of the TLR7-associated signaling cascade.

Conclusion: Our findings suggest that R837 activates TLR7-mediated signaling pathways in HPASMCs, thereby promoting cell proliferation and inducing phenotypic transition.



The anti-inflammatory effect of Atractylodin in the mouse model of autoimmune hepatitis

Atractylodin 於自體免疫性肝炎小鼠模型之抗發炎效果

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Abstract

Background:

Autoimmune hepatitis (AIH) is an immune-mediated liver inflammation that leads to hepatocyte damage with progression of liver cirrhosis. Atractylodin (ATL) is a naturally derived compound extracted from the rhizome of *Atractylodes* and is noted for its antioxidant, antitumor, and immunoregulatory properties. The primary aim of this study is to evaluate ATL's impact on in the mice of AIH and to investigate its pharmacological effects and potential mechanisms.

Methods:

Concanavalin A (Con A) is used to induce AIH models in mice, resulting in severe liver inflammation and immune responses involving multiple signaling pathways and the activation of various immune cells. Mice were randomly divided into four groups (n=8): (1) normal control group; (2) vehicle (10% DMSO and 90% glyceryl trioctanoate)-Con A treatment group (Con A/V); (3) Con A-ATL 50 mg/kg treatment group (Con A/ATL 50); and (4) Con A-ATL 100 mg/kg treatment group (Con A/ATL 100). The mice in each group were euthanized; their livers and blood were collected for pathological examination.

Results:

ATL had significant anti-inflammatory effect in the mice of Con A-induced AIH. Con A induced a significant upregulation of the expression of pro-inflammatory cytokines IL-1 β , TNF- α , and IL-17 α in the liver of mice and this inflammatory effect was alleviated by ATL treatment (50 and 100 mg/kg). ATL could attenuate the apoptosis of Con A-induced AIH. The proportion of CD4 T cells secreting IFN- γ and IL-17 in the Con A group was significantly higher than that in the control group. After treatment of ATL 100 mg/kg, this inflammatory effect may be reduced.

Conclusion:

This study confirmed that ATL has powerful anti-inflammatory and immunomodulatory effects in the mice of AIH. ATL may serve as a potential therapeutic candidate for AIH.