

Oral presentation1

時間：114年11月22日(星期六)08:30-09:00

地點：台中林酒店3F環球廳 摘要：

座長/Moderator	台北慈濟醫院 陳政宏醫師 高雄榮民總醫院 曾瑞成醫師
08:30-08:42	<p>Neutrophils extracellular traps affect interferon signature in the pathogenesis of pristane-induced lupus nephritis mouse model 中性球胞外網狀結構於pristane誘發狼瘡腎炎小鼠影響干擾素標誌及其病理機轉</p> <p>Yen-Po Tsao^{1,2}, Fang-Yu Tseng², Szu-Ting Chen² 曹彥博^{1,2}, 曾方禹², 陳斯婷²</p> <p>¹ Division of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taiwan ² Institutes of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan ¹ 臺北榮民總醫院內科部過敏免疫風濕科 ² 國立陽明交通大學臨床醫學研究所</p>
08:42-08:45	Q & A
08:45-08:57	<p>Aberrant expression of TNF-α-regulated circular RNAs in T cells from patients with rheumatoid arthritis and participated to inflammatory response Ming-Chi Lu^{1,2}, Hui-Chun Yu¹, Ning-Sheng Lai^{1,2}</p> <p>¹ Division of Allergy, Immunology and Rheumatology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation ² School of Medicine, Tzu Chi University</p> <p>在類風濕性關節炎患者其T細胞中環狀核糖核酸的表現異常並參與發炎反應</p> <p>呂明錡^{1,2}, 游惠君¹, 賴寧生^{1,2}</p> <p>¹ 佛教慈濟醫療財團法人大林慈濟醫院過敏免疫風濕科 ² 慈濟大學醫學系</p>
08:57-09:00	Q & A

Neutrophils extracellular traps affect interferon signature in the pathogenesis of pristane-induced lupus nephritis mouse model

中性球胞外網狀結構於pristane誘發狼瘡腎炎小鼠影響干擾素標誌及其病理機轉

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Abstract

Background: Systemic lupus erythematosus (SLE) is characterized by a type I interferon (IFN) signature associated with persistent autoantibodies, dysregulated immune activation, and inflammation. Lupus nephritis is one of the major organ involving severe lupus patients, which also lead to great treatment challenge. Nevertheless, their direct role in triggering the type I IFN response in neutrophils and inducing neutrophil extracellular traps (NETs) remains unclear.

Methods: Intraperitoneal injection of TMPD (2,6,10,14-tetramethylpentadecane, or pristane) in C57BL/6 WT and Fas^{lpr} mice were performed. Blood was extracted and interferon signature was evaluated. Expression of levels of IFN-stimulated genes (ISGs), including ISG15, with correlation of dsDNA-ICs was measured. The involvement of gasdermin D (GSDMD) in mitochondrial pathophysiological changes and NETs formation was examined. Neutrophil infiltration, NET formation, and IgG deposition in the glomeruli were examined simultaneously. NETs deposition in glomeruli was detected with immunofluorescence staining. The effect of neutrophils inhibitor and IFNAR blocker on IFN signature and disease progression was evaluated. The effect of the GSDMD inhibitor, disulfiram (DSF), for securing the mitochondrial membrane potential and preventing mtDNA cytosolic leakage was tested.

Results: Increasing GSDMD cleavage was detected in pristane treated mice, and the increasing serum MPO-DNA could be detected as well. dsDNA-ICs containing serum stimulation activate the Caspase-4-GSDMD axis, promoting N-GSDMD mitochondria outer membrane targeting. Through the staining of interferon signature, increasing neutrophils infiltrating and ISG15 signaling were noted in kidney sections, with concomitant IgG deposition and structural damages. Excessive NET formation was observed, associated with the appearance of type I IFN signature, inflammatory markers, and podocyte loss, which were ameliorated after DSF treatment. The signal intensity of ISG15 in the kidney of lupus-prone mice was profoundly reduced after DSF treatment, with subsequent improvement in proteinuria and glomerular inflammation. Similar findings could be noted after treatment of IFNAR blocker.

Conclusion: These findings highlight the crucial role of IFN-I production, activating the CASPASE4-GSDMD axis, increasing neutrophils activation may have crucial role in the pathogenesis of lupus nephritis. The tight association between interferon signature, neutrophil activation, and the progression of lupus nephritis was evidenced in the mouse model.

Aberrant expression of TNF- α -regulated circular RNAs in T cells from patients with rheumatoid arthritis and participated to inflammatory response

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在類風濕性關節炎患者其T細胞中環狀核糖核酸的表現異常並參與發炎反應

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Background: We hypothesized that there are aberrant expression of circular RNAs (circRNAs) in T cells from patients with rheumatoid arthritis (RA) and participated the inflammatory responses.

Methods: The expression profile of circRNAs in Jurkat cells co-cultivated with/without TNF- α for 7 days were analyzed by the next generation sequence (NGS) and then validated by the real-time polymerase chain reaction. The potential differences in chronic TNF- α exposure affected circRNA expression in T cell samples from RA patients and controls were investigated. The expression levels of circRNAs was correlated to DAS28 scores of RA patients. The transfection study was carried out to study the functions of the specific circRNA.

Results: Following NGS analysis, we found that over-expression of 83 circRNAs and under-expression 292 circRNAs in Jurkat cells after co-culture with TNF- α for 7 days. After validation, we found the expression levels of 21 circRNAs were consistently decreased in Jurkat cells after co-culture with TNF- α for 7 days. In these chronic TNF- α exposure-affected circRNAs, the expression levels of 11 circRNAs were significantly decreased in RA T cells and the expression levels of four of the circRNAs were associated with DAS28 scores of RA patients. Overexpression of specific circRNA, but not its linear form, increased the phosphorylation of STAT3 and AKT, resulting increased secretion of IFN- γ and IL-2 in activated Jurkat cells via targeting PP2A.

Conclusion. We found there are aberrant expression of TNF- α -regulated circular RNAs in RA T cells. The expression of some circRNAs correlated with DAS28 scores of RA patients. Transfection of circRNAs affected the T-cell signaling pathway. CircRNAs did participated the pathogenesis of RA.