免疫學新知專題研討會

Advances in immune pathogenesis and development of new treatment for systemic lupus erythematosis (SLE)

時間：112 年 5 月 13 日（星期六）14:00-17:00

地點：台大醫學院 103 講堂

主辦：中華民國免疫學會

Time	Topic	Speaker	Moderator
13:30-14:00	Registration		
14:00-14:20	The development of new therapeutic targets in SLE	許秉寧 台大醫院內科部/台大醫學免疫所	許秉寧 台大醫學院內科/免疫所
14:20-15:00	Innate immune checkpoint NLRP12 represses IFN signatures and attenuates lupus nephritis progression	陳斯婷 陽明交通大學臨床醫學研究所	
15:00-15:20	Coffee Break		
15:20-16:00	Recent advances in emerging new treatment in SLE	陳明翰 台北榮總內科部	陳明翰 台北榮民總醫院內科部
16:00-16:40	From small molecule compound research to development of new drug treatment in lupus nephritis	劉峰誠 三軍總醫院內科	
16:40-17:00	Closing and Conclusion remark		許秉寧 台大醫學院內科/免疫所

The development of new therapeutic targets in SLE

台大醫院內科部/台大醫學免疫所　許秉寧

New therapeutic targets are desperately needed for patients with SLE. Indeed, only anifrolumab and the B-cell growth factor inhibitor belimumab have been approved for treatment of SLE, and these drugs aren't effective for all patients. The dearth of approvals is not for want of trying. Many drugs that showed promise in phase 2 studies were unsuccessful in phase 3 studies, reflecting the huge financial and scientific investment that has gone into addressing unmet need for patients with SLE. Unsuccessful trials have been blamed on ineffective trial design and poorly thought-out inclusion criteria, but they also reflect researchers' lack of understanding of why SLE develops and whether causative pathways differ from patient to patient. These complexities make the identification of a single causative mutation even more attractive, but the reality of SLE is rarely this simple. In most cases, a whole host of environmental, hormonal, genetic, and epigenetic factors are probably at play in individuals who are susceptible to SLE. Indeed, more than 100 genetic polymorphisms have been shown to contribute to the disease.

The results pointed to key roles for several immune cell populations: naive CD4 T cells, which were less numerous in patients with SLE, particularly those of east Asian descent, regardless of background medications; and monocytes and B cells, which harboured the majority of SLE risk variants. The insights from this technique are in their infancy, but they have already highlighted that the cellular and biological context is key, and they will likely reveal important clues for why specific treatments work well in some people but not others. As more evidence points to varying molecular signatures and the role of ethnicity in driving disease differently, it is exciting and encouraging that there seems to be an explosion of research into the biology of SLE and more tools at researchers' disposal.

Innate immune checkpoint NLRP12 represses IFN signatures and attenuates lupus nephritis progression

陽明交通大學臨床醫學研究所　陳斯婷

Signaling driven by nucleic acid sensors participates in interferonopathy-mediated autoimmune diseases. NLRP12, a pyrin-containing NLR protein, is a negative regulator of innate immune activation and type I interferon (IFN-I) production. Peripheral blood mononuclear cells (PBMCs) derived from systemic lupus erythematosus (SLE) patients expressed lower levels of NLRP12, with an inverse correlation with IFNA expression and high disease activity. NLRP12 expression was transcriptionally suppressed by runt-related transcription factor 1–dependent (RUNX1-dependent) epigenetic regulation under IFN-I treatment, which enhanced a negative feedback loop between low NLRP12 expression and IFN-I production. Reduced NLRP12 protein levels in SLE monocytes was linked to spontaneous activation of innate immune signaling and hyperresponsiveness to nucleic acid stimulations. Pristane-treated Nlrp12–/– mice exhibited augmented inflammation and immune responses; and substantial lymphoid hypertrophy was characterized in NLRP12-deficient lupus-prone mice. NLRP12 deficiency mediated the increase of autoantibody production, intensive glomerular IgG deposition, monocyte recruitment, and the deterioration of kidney function. These were bound in an IFN-I signature–dependent manner in the mouse models. Collectively, we reveal a remarkable link between low NLRP12 expression and lupus progression, which suggests the impact of NLRP12 on homeostasis and immune resilience.

Recent advances in emerging new treatment in SLE

台北榮總內科部　　陳明翰

The failure of many new, mostly biologic, drugs to meet their primary end points in double-blind clinical trials in patients with systemic lupus erythematosus (SLE) has caused a profound sense of disappointment among both physicians and patients. Arguably, the success of B cell depletion with rituximab in open-label studies and in patients with lupus nephritis in the USA and in difficult-to-treat patients with SLE in the UK, together with the approval of belimumab (which blocks B cell-activating factor (BAFF)) for use in patients with SLE and the recognition that clinical trial design can be improved, have given some cause for hope. However, changes to therapies in current use and the development of new approaches are urgently needed. The results of the latest studies investigating the use of several new approaches to treating SLE are discussed in this symposium, including: fully humanized anti-CD20 and anti-CD19 monoclonal antibodies; inhibition of tyrosine-protein kinase BTK; CD40 ligand blockade; interfering with the presentation of antigen to autoreactive T cells using a peptide approach; a receptor decoy approach using an analogue of Fcγ receptor IIB; dual blockade of IL-12 and IL-23; and inhibition of Janus kinases.

Evidence also exists to support a genetic association between SLE and type I interferon-associated genes, and a high prevalence of ‘drug-induced SLE’ occurs in patients receiving therapeutic IFNα. Together, these findings have promoted a strong interest in developing agents targeting type I interferons for use in SLE.

From small molecule compound research to development of new drug treatment in lupus nephritis

三軍總醫院內科　劉峰誠

The limitations of current drug screening methods for autoimmune diseases have led to the need for alternative methods to improve the accuracy and efficiency of drug discovery. Animal models and high-throughput drug screening platforms have limitations in predicting drug efficacy and safety in humans, and there is a need for more accurate and efficient drug screening methods. AI decision support systems offer a promising solution by developing a drug screening platform that can predict drug efficacy and safety in humans, thus improving clinical care. The development of effective drugs for systemic lupus erythematosus (SLE), a complex autoimmune disease that affects multiple organs and tissues, has been challenging due to the heterogeneity of the disease and the lack of reliable biomarkers to predict treatment response. Traditional drug development for SLE often involves animal testing, but there is growing interest in using artificial intelligence (AI) to reduce the need for animal testing and accelerate the drug discovery process.

The use of AI decision support systems in drug discovery and development offers a promising solution to reduce the need for animal testing, accelerate the drug discovery and repurposing process, and improve the accuracy of drug screening for autoimmune diseases such as SLE. The development of alternative methods such as in vitro models and computational modeling, and safety assessment using computational models, can further reduce the use of animal testing in drug screening.