

investigate the left ventricular diastolic function and the factors related in SLE patients compared with healthy controls.

Methods Thirty consecutive female SLE patients without evidence of cardiac disease were underwent standard transthoracic echocardiography, and were compared with 30 age-matched healthy female controls. Patient characteristics, organ damage and laboratory data were retrieved by medical chart review.

Results In SLE patients, indexes of LV diastolic function differed from control group, with reduced early diastolic filling velocity (E), as well as prolongation of the time taken from the maximum E point to baseline, reduced ratio of early to late diastolic flow velocity (E/A), prolonged ratio of E to early diastolic mitral annular velocity (E') (E/E'). However, the differences did not show statistical significance. Anti-Ro antibody positivity was observed in 43% of SLE patients, and it was correlated with higher E/A ratio significantly (1.3 ± 0.4 vs 1.0 ± 0.2 , $p=0.03$). In addition, the SLE patients with hematologic or renal involvement showed more enlarged size of left atrium significantly compared to the patients without any involvement (36 ± 4.3 vs 31 ± 9.2 , $p=0.01$).

Conclusions Although not statistically significant, there was a trend which suggested that patients with SLE have subclinical impaired diastolic function compared with the healthy control. Presence of anti-Ro antibody and systemic organ involvement was related with the diastolic dysfunction markers.

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EDA+ FIBRONECTIN IN TUBULO-INTERSTITIAL INJURY IN LUPUS NEPHRITIS

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Background and aims Anti-dsDNA antibody plays a critical role in the pathogenesis of lupus nephritis and contributes to inflammatory and fibrotic processes in the kidney. EDA⁺ spliced variant of fibronectin (EDA⁺ FN), normally only weakly expressed, is markedly increased in pathological conditions. We investigated the effect of human polyclonal anti-dsDNA antibodies on the expression of EDA⁺ FN in proximal tubular epithelial cells (PTEC) and the functional consequence.

Methods EDA⁺ FN expression in human renal biopsies of Class III/IV±V lupus nephritis was assessed by cytochemistry. Cultured PTEC were incubated with control IgG or IgG anti-dsDNA antibodies isolated from lupus nephritis patients for 24 hour and the expression of EDA⁺ FN was investigated. Recombinant human EDA peptide was used to investigate the functional role of EDA⁺ FN in PTEC.

Results The results showed that EDA⁺ FN was absent from normal kidney tissue but was markedly increased in the tubulo-interstitium in lupus nephritis patients. Cultured PTEC constitutively expressed native FN but not EDA⁺ FN. Anti-dsDNA antibodies, compared with serum-free-medium and control IgG, increased EDA⁺ FN expression by 5.8- and 5.6-fold respectively ($p<0.05$ for both), and the induction was mediated through PI3K and mTOR activation. Exogenous IL-1 β and TGF- β 1, but not IL-6, IL-8 or MCP-1, induced EDA⁺ FN by 1.8- and 2.3-fold respectively. Recombinant EDA peptide increased native FN, collagen I, laminin and SNAIL expression, but decreased E-cadherin expression, in PTEC.

Conclusions Our data demonstrated a role of EDA⁺ FN in the pathogenesis of tubulo-interstitial disease in lupus nephritis.

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JOINT DEPOSITED IGG INDUCES ARTHRITIS BUT INHIBITS OSTEOCLASTOGENESIS IN SLE THROUGH SYK

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Background and aims Although arthritis is frequent in patients with systemic lupus erythematosus (SLE), its pathogenesis remains unclear. The aim in our study is to investigate the pathogenesis of arthritis in SLE.

Methods We analysed the feature of SLE patients with arthritis and lupus-prone mice with arthritis, investigated the role of joint deposited IgG in the development of lupus arthritis.

Results Arthritis lacking bone erosion is common symptom in most of SLE patients and spontaneously develops in lupus prone mice. Large amount of IgG deposited in joint of lupus prone mice. Similar arthritis to lupus prone mice was induced by intraarticular injection of lupus IgG and was dependent on the dose of lupus IgG. Joint deposited IgG, monocytes/macrophages and TNF α were required in the development of lupus arthritis. Joint deposited lupus IgG inhibited RANKL-induced osteoclastogenesis in dose and time dependent manner. Lacking ITAM containing Fc γ RIII reduced inhibitory effect of lupus IgG on osteoclastogenesis. Lupus IgG quickly stimulated Syk activation than RANKL through lipid rafts. Lupus IgG-induced Syk activation is related to dsDNA Ab. Blocking of Syk significantly inhibited arthritis induced by lupus IgG and arthritis in lupus prone mice, suppressed Syk activation induced by lupus IgG and osteoclastogenesis induced by RANKL.

Conclusions The joint deposited IgG exerts an important role in the development of lupus arthritis lacking of bone destruction, Syk plays a crucial role in lupus IgG-induced arthritis and inhibited osteoclastogenesis. This finding will promote development of effective therapeutic strategy to arthritis in SLE patients.

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OESTROGEN PROMOTES SLE SERUM IGG-INDUCED SKIN INFLAMMATION VIA THE OESTROGEN MEMBRANE RECEPTOR GPER1

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Background and aims Skin injury is the second most common clinical manifestation in patients with systemic lupus erythematosus (SLE). Oestrogen may affect the onset and development of SLE. This study was undertaken to elucidate the role of oestrogen in the development of SLE skin injury.

Methods We investigated the role of oestrogen and its membrane receptor GPER1 in SLE-related skin injury in mice treated with SLE serum *in vivo*, and monocytes from mouse spleen *in vitro*.

Results We found that skin injury induced by SLE serum was more severe in female mice and required monocytes. E2

promoted these effects through the membrane receptor GPER1 located in lipid rafts and that inhibition of lipid rafts and GPER1 suppressed SLE serum-induced skin inflammation and expression of inflammatory molecules.

Conclusions We conclude that oestrogen promotes the development of skin injury induced by SLE serum through the membrane receptor GPER1 and that lipid rafts play an important role in the regulatory effect of GPER1 in SLE skin inflammation.

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THE MAJOR ROLES OF MONOCYTES AND THEIR PRODUCT TUMOUR NECROSIS FACTOR ALPHA IN THE INDUCTION OF SKIN INFLAMMATION TRIGGERED BY INTRADERMAL LUPUS IGG

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Background and aims Skin injury is the second most common clinical manifestation in patients with systemic lupus erythematosus (SLE), but its pathogenesis has not been thoroughly elucidated.

Methods Based on skin deposition of IgG in SLE, we studied the features and mechanisms of intradermal IgG-induced skin inflammation

Results We found that skin inflammation appeared at 3 hour and peaked at 3 d after intradermal injection of lupus IgG. This phenomenon was related to the dose of injected IgG but not to systemic disease activity. The severity of skin inflammation induced by lupus IgG was significantly decreased in mice depleted of monocytes and in mice deficient in TNF- α but not in mice lacking mature lymphocytes. Furthermore, lupus IgG promoted the progression of monocyte differentiation to dendritic cells (DCs) and enhanced the expression of TNF- α . TNF- α was found to stimulate the IgG-induced maturation of DCs and played a major role in the proliferation and activation of keratinocytes.

Conclusions The results also indicate that the deposition of IgG in skin exerts an important role in the pathogenesis of skin injury in patients with SLE; therefore, blocking the IgG/FcR signalling pathway can be a therapeutic target in skin lesions of patients with SLE.

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THE ROLE OF IL-1 IN SKIN INFLAMMATION INDUCED BY LUPUS SERUM IGG

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Background and aims Systemic lupus erythematosus (SLE) is a seriously chronic autoimmune disease, which is characterised by a large number of autoantibodies and multiple organ damage. Skin lesion is one of the common clinical manifestations of lupus erythematosus, but its pathogenesis is not clear. IL-1 is a proinflammatory cytokine, the aim in this study is to investigate the role of IL-1 in the skin injury in SLE.

Methods We used IL-1 receptor deficient mice and other gene deficient mice to study the role of IL-1 in the lupus serum IgG -induced skin inflammation.

Results We found that the severity of skin lesion in IL-1 receptor deficient mice and caspase-1 deficient mice was reduced compared with that in wild type mice. IL-1 receptor deficiency suppressed the expression of Fc γ RI (CD64) and MHC class II (CD74), and increased the level of Fc γ RII (CD32) induced by lupus serum. IL-1 receptor deficiency also suppressed the lipid raft clustering and IFN- γ in T cells, and reduced IgG internalisation and presentation in macrophage, and decreased expression of MCP-1 and TNF α in monocytes. In addition, TNF α could promote the proliferation of keratinocytes.

Conclusions Our findings indicate that IL-1 plays an important role in skin lesions of lupus erythematosus. This study suggests IL-1 is a therapeutic target in skin lesions of systemic lupus erythematosus.

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HEPATIC DEPOSITED IGG MEDIATED LIVER DAMAGE THROUGH KUPFFER/NATURAL KILLER CELLS AND THEIR PRODUCTS

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Background and aims Hepatic disorders are frequent in patients with systemic lupus erythematosus (SLE), yet the aetiology and pathogenesis of liver injury in SLE remains unclear. The present study primarily aimed to understand the cellular and molecular mechanisms involved in the expression of liver damage in SLE.

Methods We analysed clinical and serological characteristics of 404 SLE patients with liver dysfunction, and determined the pathogenesis of liver damage in SLE by using lupus-prone mice and a novel animal model of liver injury induced by lupus serum IgG.

Results 22.5% of SLE patients have liver dysfunction, and even 38% of them have lupus-hepatitis. There are a large amount of inflammatory cells around the portal areas of the livers, apoptotic hepatocytes and IgG deposition in the liver in lupus-prone mice. Liver injury was successfully established by intrahepatic injection of lupus serum IgG. Immune complexes (ICs) stimulated Kupffer cells (KCs) to secrete TNF- α involved in the development of inflammation and apoptosis in liver. IFN- γ produced by activated natural killer cells (NKs) directly mediated liver damage and also enhanced the TNF- α -mediated apoptotic pathway. The depletion of KCs and NKs abolished apoptosis induced by ICs in liver, suggesting that KCs and NKs have a synergic effect on liver injury.

Conclusions Our findings demonstrated that liver injury was induced by hepatic IgG deposition in SLE and innate immune cells and their products exert an important role in the development of liver injury in SLE. Our results may promote to develop potential therapeutic strategies in prevention and treatment of liver injury in SLE.

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RHUPUS SYNDROME : A CASE REPORT AND LITERATURE REVIEW

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