THU0241

LUPUS PROGRESSION IS PREVENTED BY TREATMENT WITH VERDINEXOR, AN INHIBITOR OF THE NUCLEAR EXPORT PROTEIN EXPORTIN-1, BY LIMITING GERMINAL CENTER FORMATION AND DEVELOPMENT OF AUTOACTIVE ANTIBODY SECRETING CELLS

Javier Rangel-Moreno¹, Nida Meednu¹, Douglas Widman², Savanna Gornisiewicz², Sharon Tamir², Jennifer H. Anolik¹. ¹University of Rochester School of Medicine, Division of Allergy, Immunology and Rheumatology, Rochester, United States of America; ²Karyopharm Therapeutics, Grants Management, Newton, United States of America

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by simultaneous activation of the innate and adaptive arms of the immune system. Recently the nuclear export protein exportin-1 (XPO1) has surfaced as an attractive target for the treatment of SLE and other autoimmune disorders. Selective Inhibitor of Nuclear Export (SINE) compounds are potent, orally available and well-tolerated XPO1 inhibitors. SINE compounds inhibit the nuclear export of over 220 cargoes, and this pleiotropic effect on multiple signaling pathways exerts apoptotic and anti-inflammatory effects, particularly in dampening the NF- κ B response. Based on previous studies with different SINE compounds, we decided to define the minimal amount and frequency of verdinexor treatment necessary to maintain disease inhibition after induction therapy. **Objectives:** The primary objective of this study was to examine the ability of verdinexor to control the formation of germinal centers and limit the numbers of autoreactive antibody secreting cells (ASC) in a NZB/NZW F1 murine model of SLE.

Methods: To evaluate the minimal efficacious dose of SINE compounds in a preclinical recovery model of SLE, cohorts of lupus-prone mice with established disease (elevated anti-dsDNA antibody titer and proteinuria) were dosed with SINE compound or vehicle for eight weeks, at which time treatment groups were stratified, and escalating administration schedules (both dose and frequency) of verdinexor were examined for their ability to control recurrent disease. We used flow cytometry to enumerate dsDNA antibody-secreting cells (ASC) in the spleen and bone marrow and immunofluorescence to visualize germinal centers (GC) in spleen.

Results: We found that following induction therapy, treatment with verdinexor significantly maintained disease inhibition effectively at 7.5mg/kg administered weekly. Concomitantly, we observed significantly decreased levels of GC B cells, plasma cells and plasmablast levels in the bone marrow and the spleen 4 weeks after treatment groups were stratified. The potent effect of SINE compound monotherapy on GC and auto-reactive ASC showed that a pronounced elimination of GC and auto-reactive ASC is achieved after 4 weeks of maintenance therapy administered once weekly. When combined with a proteasome inhibitor (PI), short-term verdinexor plus PI treatment resulted in a synergistic effect, resulting in a significant reduction in the number of auto-reactive antibody secreting cells (ASC).

Conclusion: Verdinexor has demonstrated efficacy in a murine induction/disease inhibition model of SLE by reducing generation, survival and function of auto-reactive immune cells. It is likely that inhibition of the canonical NF- κ B pathway underlies verdinexor's inhibitory effect. The reversible impact of SINE compounds on SLE (symptoms return when therapy is removed) provides a potential window of time for immunization of lupus patients. Together, our findings suggest the potential of SINE compounds to have a significant impact on disease progression in SLE.

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THU0242

MIR-326 OVEREXPRESSION IN T CELLS BREAKS TH17/TREG BALANCE IN MRL/LPR MICE

Yuan Xia, Xuan Fang, Nan Xiang, Xiaojuan Dai, Li Jin, Li Xiaomei, Jinhui Tao, Li Xiangpei. The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Department of Rheumatology and Immunology, Hefei, China

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs leading to tissue damage¹. T lymphocytes have been recognized as key contributors to disease pathogenesis². Inflammatory Th17 subsets promote inflammation, while defects in regulatory T cells (Tregs) lead to unchecked immune responses³. Emerging

data suggest that single miR species can profoundly alter the phenotype and outcome of immune responses in SLE⁴.

Objectives: we describe a role for miR-326 in driving deregulation of Th17/Treg balance in lupus mouse and highlight therapeutic advances of miR-326.

Methods: 3 groups of female MRL/lpr mice were injected with lentivirus-miR-326 (LV-326) or lentivirus-miR-326 specific inhibitor (LV-sponge) to increase or inhibit miR-326 expression, respectively, and lentivirus-no-encoding (LV-ctrl) as control, 10 mice per group. The percentage of Th17 cells and Tregs in spleen CD4⁺ T cells and kidney were detected by flow cytometry. The levels of serum cytokine (IL-17A, IFN- γ , TGF- β) were detected by CBA. Urinary collections (24 h) were collected and assessed for albumin using ELISA. Immunohistochemistry labeled kidney IL-17A and TGF- β expression. Differences between groups were analyzed by SPSS software.

Results: Day 7 analysis of differentiation of Th17 cells and Tregs in spleen after injection of lentivirus showed an increased percentage of Th17 in LV-326 mice, while reduction of percentage of Tregs in these mice. Testing the serum cytokines revealed that the significantly increased levels of IL-17A and IFN- γ in LV-326 mice, and decreased in LV-sponge mice, no different has been found in TGF- β between the groups. Moreover, LV-326 mice showed higher levels of 24h urinary albumin than LV-sponge and LV-ctrl mice in day 7 after injection of lentivirus. The lentivirus-miR-326 injection promoted the infiltration of Th17 cells and simultaneously increased the expression of IL-17A in kidney, no different has been found of TGF- β .

Conclusion: Our data reveal that miR-326 overexpression increased the differentiation of Th17 cells and decreased the differentiation of Tregs, and accelerated the renal injury in MRL/lpr mice. These suggest that miR-326 may play a catalytic role in the development of lupus-like changes in lupus model mouse by breaks Th17/Treg balance.

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THU0243

ROLE OF METHIONINE AND ITS TRANSPORTER CD98 IN HUMAN B CELL DIFFERENTIATION AND THE RELEVANCE TO PATHOLOGICAL PROCESSES OF SLE

Mingzeng Zhang, Shigeru Iwata, Maiko Hajime, Naoaki Ohkubo, Yasuyuki Todoroki, Hiroko Miyata, Shingo Nakayamada, Yamagata Kaoru, Yoshiya Tanaka. The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, Kitakyushu, Japan

Background: B cells play an important role in systemic lupus erythematosus (SLE). Several research protocols have focused in recent years on the topic of immunometabolism. Activation of immunocompetent cells depends on rapid synthesis of cell structure components and biomolecules, which requires enormous amounts of energy, nucleic acids and lipids. Amino acids are important ingredients of many metabolic processes. However, the role of amino acids in plasmablast differentiation and their relevance to the pathogenesis of SLE remain elusive.

Objectives: To determine the role of essential amino acids in human B cell differentiation and relevance to the pathogenesis of SLE.

Methods: In the *in vitro* arm of the study, purified CD19⁺ B cells from healthy donors were cultured with TLR7/9 ligand (LOX or CpG), IFN- α and B cell receptor (BCR) cross-linking, in the presence or absence of amino acids. We determined 1) the types of amino acids that are important for PB differentiation, 2) the amino acid transporters that are important for PB differentiation, 3) the main signaling pathway(s) involved in the presence of amino acids, 4) the transcriptional factors used in the presence of amino acids. In the clinical arm of the study, peripheral blood mononuclear cells (PBMCs) were obtained from 24 patients with RA, 35 patients with SLE, and 28 age-matched healthy controls, and

subjected to flow cytometric analysis to determine the expression of amino acids-related markers.

Results: 1) Stimulation with the combination of BCR, IFN- α and TLR7/9 ligand induced PB differentiation accompanied by uptake of amino acids. PB differentiation was abrogated in the absence of essential amino acid methionine, and to a lesser extent leucine, but not in non-essential amino acid cystine. 2) LAT1 and CD98 are known amino acid transporters. Stimulation with BCR, IFN- α and TLR7/9 ligand induced CD98 expression but suppressed LAT1 expression. CD98 expression was higher in CD27^{hi}CD38^{hi} PB than in CD27^{hi}CD38^{lo} non-PB. 3) Previous studies reported that amino acids were perceived by the sensor, leading to mTORC1 phosphorylation. However, the mechanism by which amino acids activate other intracellular signaling pathways in B cells remains elusive. We found that methionine facilitated both the BCR and mTORC1 signals. In addition, the two signals synergistically induced EZH2 expression, which is well known as a transcriptional factor for histone modification via induction of H3K27me3, in the presence of methionine. 4) Methionine induced EZH2 expression, leading to suppression of BACH2, induction of BLIMP1, XBP1 and PB differentiation. These results indicate that EZH2 is a critical factor for PB differentiation in the presence of methionine. Assessment of the expression of amino acid transporters CD98, LAT1 and EZH2 in B cells in RA and SLE patients showed overexpression of CD98 and EZH2, but not LAT1, in SLE, compared with RA and control. In SLE patients, EZH2 expression level correlated with that of CD98 in B cells. EZH2 expression also correlated with ESR and disease activity scores, such as of SLEDAI and BILAG, in SLE patients.

Conclusion: The results indicate that essential amino acid methionine plays an important role in PB differentiation through the CD98-EZH2-axis. The pathological process of SLE seems to involve essential amino acids and their metabolic/activation pathways throughout the process of PB differentiation.

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SLE, Sjögren's and APS – clinical aspects (other than treatment)

THU0244 PULMONARY MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

PLAZA NAHIA, María José Pérez, Sergio Rodríguez Montero, Carmen Trapero, Jose Luis Marengo. *Valme Hospital, Rheumatology Department, Seville, Spain*

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by inflammation and tissue damage mediated by the immune system. Respiratory manifestations are common in SLE, appearing in up to 50% of patients throughout their lives. Furthermore, it is associated with higher mortality.

Objectives: To describe the prevalence and characteristics of pulmonary involvement in patients with SLE

Methods: Observational, descriptive, cross-sectional, retrospective study performed in patients with SLE in follow-up by the Rheumatology Department of Valme Hospital. The following information is collected from medical records; age, sex, mean age at diagnosis, characteristics of pleuropulmonary involvement and ANA and antiDNA positivity.

Results: We studied 165 patients with SLE, with mean age of 37.01 $\pm$ 14.65 years, predominance of the female patients 153 (92.72%). Thirty eight of them had pulmonary involvement (23.03%), with a total of 47 episodes related to lung manifestations. Mean age at diagnosis was 39.70 $\pm$ 15.50 years. Below is shown information about lung involvement:

Variable	Prevalence	ANA +	antiDNA +	Hospitalization required
Pleuritis	19	18	5	17
Lupus pneumonitis	1	1	0	1
ILD	2	2	0	1

Shrinking lung	4	4	1	2
Pulmonary embolism	5	4	1	3
Other	16	15	9	10

Eleven patients (28.94%) presented pulmonary involvement at the time of diagnosis; pleuritis (10.63%) and only one case of interstitial lung disease, varicella pneumonia, shrinking lung syndrome, pulmonary embolism (PE) and bronchiolitis obliterans with organizing pneumonia. Two patients (4.24%) died due to severe respiratory failure secondary to bilateral pneumonia. Three of the 5 patients with PE were diagnosed with antiphospholipid syndrome secondary to SLE. Regarding treatment, most of patients who required hospitalization were in basic treatment with synthetic DMARDs (78.57% in monotherapy and 21.43% with double therapy) and only 2 patients with biologic DMARDs (Rituximab and etanercept). Six patients had no treatment because the pulmonary event was at time of diagnosis, 2 patients were with antiaggregating therapy and there was no information registered in two patients (episode before 1997). 91.10% of the patients presented positive for ANA, of which 37.14% (13 patients) also presented positive antiDNA. No information was collected about autoimmunity in one patient (2.12%).

Conclusion: Pulmonary involvement in SLE is prevalent, although a significant proportion may remain asymptomatic. The little prevalence of pulmonary manifestations in our series might be due to low mean age, according to the result of a recent systematic review where analysed more than 10000 patients and concluded pulmonary manifestations are more frequent in late-onset SLE. The differential diagnosis is broad and the infectious cause, the main cause of mortality in patients with SLE, must always be ruled out.

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THU0245 LOW SPECIFICITY OF THE PROPOSED 2017 ACR-EULAR CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) COMPARED TO PREVIOUS CRITERIA IN SLE PATIENTS WITH NEUROPSYCHIATRIC SYMPTOMS

Rory Monahan¹, H.J.L. Beart¹, Maka Gegeneva¹, E.G. Brilman¹, L.J.J. Beart-van de Voorde¹, César Magro Checa², Thomas Huizinga¹, G.M. Steup-Beekman¹.

¹Leiden University Medical Center, Rheumatology, Leiden, Netherlands;

²Zuyderland Medical Center, Rheumatology, Heerlen, Netherlands

Background: New ACR-EULAR SLE criteria have been proposed in order to attempt to improve classification for clinical and translational research (1, 2).

Objectives: We evaluated the performance of the proposed 2017 ACR-EULAR classification criteria in a cohort of SLE patients with neuropsychiatric (NP) symptoms and compared to previous classification criteria.

Methods: Medical records of patients visiting the NPSLE clinic of the Leiden University Medical Center (LUMC) between 2007-2017 were retrospectively evaluated. The performance of the proposed 2017 ACR-EULAR criteria, the 2012 SLICC criteria and the 1997 ACR criteria was evaluated by calculating sensitivity and specificity.

Results: 360 patients were included, of which 294 were clinically diagnosed with SLE. The newly proposed 2017 ACR-EULAR showed a sensitivity of 87% (95% CI: 83-91%) and a specificity of 74% (95% CI: 62-84%), as shown in Table 1. The 2012 SLICC criteria had a sensitivity of 85% (95% CI: 80-89%) and a specificity of 76% (95% CI: 64-85%). The 1997 ACR criteria had a sensitivity of 89% (95% CI: 85-92%) and a specificity of 89% (95% CI: 80-96%).

Sixty out of 294 patients fulfilled the proposed NP domain (delirium/psychosis/epilepsy). Using more specific criteria for NP symptoms related to SLE, as previously proposed by Bortoluzzi *et al.* (3), only 37 patients fulfilled this domain. However, this did not improve specificity, which remained 74% (95% CI: 62-84%).