Conclusion: ADAR1-mediated RNA editing is increased in active RA inducing the expression of pro-inflammatory genes thus representing a novel drug response biomarker and a potential therapeutic target in EULAR moderate/non-responders.

REFERENCES:

- [1] Stellos, et al., *Nat Med* 2016;22:1140–50. doi:10.1038/nm.4172
- [2] Liu, et al., *Nat Med* 2019;25:95–102. doi:10.1038/s41591-018-0302-5
- [3] Ishizuka, et al., *Nature* 2019;565:43–8. doi:10.1038/s41586-018-0768-9

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Novel biomarkers in RMDs – next steps towards clinical implementation

OP0298

PCSK9 IN ATHEROSCLEROTIC INFLAMMATION OF LUPUS PATIENTS AND MURINE MODEL OF LUPUS WITH ATHEROSCLEROSIS

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Background: Systemic lupus erythematosus (SLE) patients have tendencies of accelerated atherosclerosis (AS), which is refractory to statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new therapeutic target for AS for its dual mechanisms in lipids metabolism and inflammation. PCSK9 inhibitors had proved to be highly promising cardiovascular disease (CVD) drugs [1]. Our previous study suggested that Toll-like receptor 4 (TLR4) signal participates in the atherosclerotic inflammation of murine model of lupus with AS [2].

Objectives: To investigate the role of PCSK9 in atherosclerotic process of lupus and the association between TLR4 and PCSK9 in atherogenic inflammation of murine model of lupus with AS.

Table 1 Characteristics of SLE patients and controls.

Variables	SLE	Healthy controls	p-value
Number	90	50	NA
Female/Male	82/8	43/7	>0.05
Age(years)	33(29-42)	32(28-44)	>0.05
Disease duration(years)	6(3-10)	NA	NA
SLEDAI	6(2-8)	NA	NA
Cholesterol(mmol/l)	4.52(3.85-5.37)	4.52(3.93-5.60)	>0.05
LDL cholesterol(mmol/l)	2.47(1.84-3.16)	2.58(2.03-3.06)	>0.05
Triglycerides(mmol/l)	1.16(0.79-1.61)	1.34(0.87-1.56)	>0.05
HDL cholesterol(mmol/l)	1.47(1.23-1.73)	1.61(1.36-1.91)	>0.05
cIMT thickening	27/90(30.00%)	7/50(14.00%)	0.03
Treatment			
HCQ use	90/90(100%)		
Steroid use	75/90(83.33%)		
AZA use	15/90(16.67%)	NA	
CsA use	9/90(10.00%)		
MMF use	16/90(17.78%)		

Data are shown as number or median (interquartile range), respectively. SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; cIMT: carotid intima-media thickness; HCQ: Hydroxychloroquine; AZA: Azathioprine; CsA: Cyclosporin A; MMF: Mycophenolate Mofetil.

Methods: 90 SLE patients and 50 healthy controls were included. According to carotid intima-media thickness (cIMT), SLE patients were further divided into SLE-AS and SLE-NonAS subgroups (cut-off point: 1.0mm). Traditional CVD risk factors, inflammatory biomarkers and PCSK9 concentrations were compared

between: (I) SLE patients and controls; (II) SLE-AS subgroup and SLE-NonAS subgroup. Correlational analysis and multivariate linear regression analysis were applied to analyze the association between PCSK9 levels and disease parameter, and the predictors of PCSK9 levels in SLE patients. Effects on PCSK9 concentrations by monotherapy with hydroxychloroquine (HCQ), which is thought having protective effects against CVD in SLE, were investigated by follow-up analysis in 15 SLE patients with inactive disease (SLEDAI=2). In animal experiment, murine model of SLE with AS was set up by intraperitoneally injection of lipopolysaccharides (LPS) in ApoE^{-/-} mice. 30 female ApoE^{-/-} mice were respectively administered with LPS (SLE+AS group, n=10), saline (AS group, n=10) and LPS plus injection of lentiviruse-PCSK9 small hairpin RNA targeting the mouse PCSK9 gene into the tail vein to interfere PCSK9 expression (SLE+AS+PCSK9i group, n=10). 10 female C57BL/6 mice were included as controls. Serum concentrations of PCSK9 and inflammatory biomarkers including TNF- α and IL-1 β , atherosclerotic lesion, lipids parameters, expression of PCSK9, TLR4 and NF- κ B p65 in atherosclerotic plaque were assessed.

Results: Characteristics of SLE patients and controls were listed in Table 1. SLE patients had significantly elevated serum PCSK9 levels than controls, especially in SLE-AS subgroup, accompanied with higher ratio of cIMT thickening. Correlational analysis showed PCSK9 concentrations correlated with C-reactive protein (CRP) levels, age and erythrocyte sedimentation rate (ESR), but not lipids parameters. Univariate and multivariate linear regression revealed that only CRP, but not age or ESR was positive predictors of PCSK9. Monotherapy with HCQ for 3 months significantly reduced PCSK9 levels in inactive SLE patients (Table 2, Figure 1). Mice in SLE+AS group had significantly higher serum PCSK9 concentrations than mice in AS group and C57BL/6 mice. Immunohistochemistry showed that PCSK9 overexpression was observed in SLE+AS mice than those in AS group and SLE+AS+PCSK9i group. Mice in SLE+AS+PCSK9i group exhibited decreased inflammatory cell infiltration in atherosclerotic plaque, alleviated atherosclerotic lesion, lower serum TNF- α and IL-1 β levels and attenuated expression of TLR4 and NF- κ B p65 in atherosclerotic plaque than SLE+AS group. PCSK9 silencing had no significant effects on lipids parameters in SLE+AS mice (Figure 2).

Table 2 Multivariate linear regression of CRP, ESR, age (independent variable) and PCSK9 (dependent variable) in SLE patients

Model	Unstandardized Coefficients B	Std. Error	Standardized Coefficients Beta	t	p
(Constant)	280.339	72.128		3.887	<0.001
CRP	4.040	0.972	0.408	4.158	<0.001
ESR	1.028	0.974	0.103	1.055	0.294
Age	2.931	1.767	0.159	1.659	0.101

SLE: systemic lupus erythematosus; PCSK9: Proprotein convertase subtilisin/kexin type 9;

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Figure 1. (a)-(b) SLE patients had significantly elevated serum PCSK9 concentrations than controls, especially in those with AS; (c) Monotherapy with HCQ for three months significantly reduced PCSK9 levels in SLE patients with inactive disease(n=15); (d)-(f) Difference of age, ESR and CRP levels between patients in SLE-AS subgroup and those in SLE-NonAS subgroup had statistical significance; (g)-(i) Correlational analysis showed that serum PCSK9 levels correlated with age, CRP levels and ESR in SLE patients.

Figure 2. (a) SLE+AS mice had significantly higher serum PCSK9 concentrations than mice in AS group and C57BL/6 mice; (b) (c) Expression of PCSK9 was interfered via injection of lentivirus-PCSK9 small hairpin RNA targeting the mouse PCSK9 gene into the tail vein. Compared with SLE+AS group(b), SLE+AS+PCSK9i group(c) exhibits bright green fluorescence in atherosclerotic plaque; (d) (e) Immunohistochemistry showed that PCSK9 overexpression was observed in SLE+AS mice than those in AS group and SLE+AS+PCSK9i group. Mice in SLE+AS+PCSK9i group showed alleviated inflammatory cell infiltration and atherosclerotic lesion than those in SLE+AS group and AS group(d-f); Immunohistochemistry of PCSK9, $\times 200$; g-i: Oil red O stain, $\times 40$; (j) Mice in SLE+AS+PCSK9i group exhibited lower serum TNF- α and IL-1 β levels and attenuated expression of TLR4 and NF- κ B p65 in atherosclerotic plaque than those in SLE+AS group; (m) (p) PCSK9 silencing had no significant effect on lipids parameters(TCHO, LDL-C, TG and HDL-C) in SLE+AS mice($p>0.05$).

Conclusion: PCSK9 participates in atherogenic inflammation in SLE patients and murine model of SLE with AS. This process is associated with TLR4-NF- κ B pathway, probably independent of lipids parameters alteration. HCQ can effectively reduce PCSK9 levels in SLE patients.

REFERENCES:

- [1] Sabatine MS, et al. N Engl J Med. 2017; 376(18):1713-1722.
- [2] Ni JQ, et al. Clin Dev Immunol. 2013;2013:476856.

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OP0299

ASSESSMENT OF ROLE OF URINARY HEPARANASE IN LUPUS NEPHRITIS PATIENTS AND ITS CORRELATION WITH DISEASE ACTIVITY

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Background: Lupus nephritis (LN) is one of the most common and serious complication of Systemic Lupus Erythematosus (SLE) and assessment of its activity is crucial. Heparanase has been proposed to be important in the pathogenesis of proteinuria in various forms of glomerulonephritis.

Objectives: To assess the ability of urinary heparanase to identify SLE with nephritis and the relation of this marker to lupus activity.

Methods: This cross sectional study was carried out on 90 subjects; 70 patients with SLE and 20 healthy volunteers as a control. All patients and controls were subjected to full history taking and complete clinical examination, routine investigations. Immunological assay and assessment of disease activity by systemic lupus erythematosus disease activity index (SLEDAI) score, renal SLEDAI (r-SLEDAI) were done for lupus nephritis group. The lupus patients were divided according to SLEDAI score into 4 groups; 20 with active lupus nephritis, 17 with non-active LN, 18 with active lupus without renal involvement, 15 with non-active lupus without renal involvement. Urinary Heparanase levels were measured by using ELISA for all groups.

Results: The level of urinary heparanase was significantly higher in LN groups than non-LN groups and control. It was also significantly higher in active LN than non-active LN patients. There was a significant positive correlation between urinary heparanase and 24 hours urinary proteins, total SLEDAI, and r-SLEDAI, and significant negative correlation between urinary heparanase and C3 & C4. ROC curve analysis revealed that urinary heparanase predicted presence of lupus nephritis activity with a sensitivity of 80%, and a specificity of 91.43%.

Conclusion: Urinary heparanase levels are increased in patients with active LN and correlate with disease activity markers, indicating that it can serve as a new useful biomarker for lupus nephritis activity.

REFERENCES:

- [1] Kim K-J, Kim J-Y, Park S-J, Baek I-W, Yoon C-H, Kim W-U, et al. SAT0227 Urinary heparanase activity is elevated in patients with lupus

nephritis and correlate with protein excretion. Annals of the Rheumatic Diseases. 2013;71(Suppl 3):548-9.

- [2] Cho C, Kim K, In-Woon B. 206 Increased urinary heparanase levels are associated with active lupus nephritis. Archives of Disease in childhood; 2017.

Table (1). : Comparison between the different studied groups regarding HPSE (ng/ml)

	Group I Active LN (n=20)	Group II Non active LN (n=17)	Group III Active lupus Without nephritis (n=18)	Group IV Non-active lupus Without nephritis (n=15)	Group V Control (n=20)	F	P
HPSE (ng/ ml)	2.36 $\pm$ 0.62	1.44 $\pm$ 0.11	1.23 $\pm$ 0.07	1.31 $\pm$ 0.07	0.29 $\pm$ 0.13	115.716*	<0.001*
p ₁	<0.001*	<0.001*	<0.001*	<0.001*			
Sig. bet.	p ₂ <0.001*,	p ₃ =0.914,	p ₄ <0.001*,	p ₅ =0.719,	p ₆ <0.001*,		p ₇ =0.230
Grps							

F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)

- p: p value for comparing between the different groups
- p₁: p value for comparing between group V and each other group
- p₂: p value for comparing between group I and group II
- p₃: p value for comparing between group III and group IV
- p₄: p value for comparing between group I and group III
- p₅: p value for comparing between group II and group IV
- p₆: p value for comparing between group I and group IV
- p₇: p value for comparing between group II and group III

Table 2. Agreement (sensitivity, specificity) for HPSE (ng/ml) to diagnose active lupus nephritis

	Cut off	Sensitivity	Specificity	PPV	NPV
HPSE (ng/ ml)	>1.48	80.0	91.43	72.7	94.1
HPSE (ng/ml)					
AUC				0.877	
p				<0.001*	
95% C.I				0.771 – 0.982

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OP0300

A NEUTROPHIL SIGNATURE IS STRONGLY ASSOCIATED WITH CARDIOVASCULAR RISK IN GOUT

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Background: Similar to other rheumatic diseases, patients with gout have an increased cardiovascular morbidity and mortality, not fully explained by traditional cardiovascular risk factors. Instead, gout-specific factors, including xanthine oxidase induced oxidative stress, increased lipid oxidation and chronic low-grade inflammation, have been suggested as important contributors.(1) Neutrophils, through formation of neutrophil extracellular traps (NETs), partake in pro-