

Innate immunity in rheumatic diseases

AB0051

SERUM AMYLOID A AND PENTRAXIN 3: INNATE IMMUNE RESPONSE AND DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that involves several molecular patterns with a wide spectrum of clinical manifestations and symptoms. Inflammation and related pathway play a role in SLE pathogenesis. The pentraxin superfamily including long and short pentraxin, C Reactive Protein CRP, Serum amyloid A (SAA), Pentraxin 3 (PTX3) are key components of innate immune system and induce a variety of inflammation associated pathway. However Literature provides several evidences that CRP serum levels not correlated with clinical and immunological manifestations. This situation affected clinical practice and the patient follow up. PTX3 have been identified as a component of inflammatory status in several autoimmune conditions. SAA is an acute phase protein secreted in large quantity during inflammation.

Objectives: We want to evaluated SAA, PTX3 and CRP concentrations, their correlation between SLE Disease Activity Index (SLEDAI), that including complement fractions C3, C4.

Methods: We enrolled fifty patients that fulfilled the SLE American College of Rheumatology criteria and fifty healthy subjects. The SLE disease activity was classified with the SLEDAI (0 to 12). Patients were divided into two groups according to SLEDAI score: inactive group (Group 1, 25 patients, 50%: SLEDAI < 4) and active group (Group 2, 25 patients, 50%: SLEDAI 5 to 12). PTX3 concentration was measured by a sandwich ELISA kit (Hycult) with 2.8ng/mL cut-off point. SAA concentration was detected by nephelometry performed on a BN ProSpec System (Siemens, Germany), with assay kit based on polyclonal antibodies (Siemens Healthcare Diagnostics Products, Germany, 6.5mg/L cut-off point). High sensitive CRP concentrations were determined using the ci8200 platform (Abbott Laboratories Chicago, Illinois).

Results: Plasma PTX3 and serum SAA levels was significantly higher in SLE patients than in the healthy subjects (PTX3 11.5 ± 7.3 ng/mL vs 2.3 ± 1.1 ; $p < 0.001$; SAA: 87 ± 77 mg/L vs 2.6 ± 2.5 ; $p < 0.001$). These differences were not evident in CRP levels (8.5 ± 7.8 mg/L vs 6.2 ± 2.5). Considering two groups, there were statistical differences in PTX3 level (Group 2: 14.9 ± 12 ng/mL vs Group 1: 2.16 ± 0.5 ng/mL, $p < 0.05$) and SAA concentration (Group 2: 114 ± 89 ng/mL vs Group 1: 3.6 ± 1.7 ng/mL, $p < 0.05$) but not in CRP concentration (Group 2: 11.5 ± 8.4 mg/L vs Group 1: 9.5 ± 3.5). There was a significantly negative correlation between C3, C4 fractions, PTX3 and SSA levels (respectively $r = -0.74$, $p < 0.05$, and $r = -0.79$, $p < 0.05$). No statistical correlation were appeared between C3, C4 fractions and CRP serum levels ($r = -0.12$, $p = 0.82$, and $r = -0.18$, $p = 0.21$). We noted a positive significant correlation between SLEDAI, PTX3 and SAA concentration ($r = 0.79$, $p < 0.05$, 0.83 , $p < 0.05$, respectively) an increase in PTX3 and SAA levels followed the lupus flare and symptoms. No significant correlation appeared between SLEDAI and CRP ($r = 0.15$, $p = 0.89$).

Conclusion: PTX3 and SAA concentration was significantly higher in SLE patients than the healthy control subjects and their levels reflected disease activity. We showed a direct correlation between PTX3 and SAA. In SLE patients PTX3 and SAA concentrations were correlated with SLEDAI. We suggest an integrate viewpoint in witch SAA and PTX3 may play a role as a biomarker of disease activity, with synergic work during SLE events. Evidences suggested that PTX3 and SAA could trigger the same molecular pathway, by TLR4, via NF- κ B.

References:

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AB0052

ROLE OF TRAINED IMMUNITY AND IMMUNOMETABOLISM IN THE PATHOGENESIS OF ERDHEIM-CHESTER DISEASE

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Background: Erdheim-Chester disease (ECD) is a chronic inflammatory disease characterized by infiltration of bone and other tissues by foamy macrophages. These cells exhibit activating mutations along the MAPK pathway, most commonly BRAFV600E, and increased production of pro-inflammatory cytokines. Although this dual neoplastic-inflammatory nature of ECD has long fascinated scientists, the mechanistic link between these two features remains elusive. We hypothesized that Trained Immunity (TI), a pro-inflammatory cell program physiologically elicited in monocytes/macrophages upon activation of the MAPK pathway, might represent the missing link between oncogenic transformation and pro-inflammatory activation in ECD.

Objectives: In this study, we aimed at determining the role of TI in the pathogenesis of ECD, and to evaluate the therapeutic potential of targeting this mechanism for the treatment of inflammation.

Methods: We developed innovative models to study ECD pathogenesis *in vitro* (based on lentiviral transduction and ectopic expression of BRAFV600E in primary human monocytes), as well as *ex vivo* (3D culture of ECD tissue biopsies in bioreactor). Functional and mechanistic features of TI, including typical changes in cell energy metabolism and epigenetics, were investigated by assessing I) cytokine and lactate production; II) mitochondrial respiration with Seahorse flux analyzer; III) glucose, glutamine and cholesterol metabolism with unbiased and targeted metabolomics analyses; IV) epigenetic changes with ChIP PCR; V) transcriptome changes with RNA sequencing.

Results: Activation of the MAPK pathway induced by BRAFV600E in macrophages induces changes in the epigenetic and gene expression landscape, cell energy metabolism, and cytokine production characteristic of TI. In particular, changes in cell energy metabolism of macrophages are characterized by increased glycolysis, glutamine metabolism, and cholesterol synthesis. This metabolic rewiring is needed to sustain rampant, constitutive production of pro-inflammatory cytokines.

Conclusion: A role emerges for TI in the pathogenesis and pro-inflammatory activation of ECD. However, maladaptive activation of this mechanism is likely common to the pathogenesis of other inflammatory and rheumatologic diseases. Since drugs targeting TI programs are already entering the clinical arena, the identification of this mechanism in the pathogenesis of inflammatory and rheumatologic conditions may promptly translate into novel, effective treatment options for affected patients.

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AB0053

BERGENIN, ACTING AS AN AGONIST OF SIRT1, REDUCE SERUM URATE IN MICE THROUGH THE UPREGULATION OF ABCG2

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Background: About 20% of individuals in the USA have asymptomatic hyperuricaemia^[1]. However, Urate-lowering therapy in asymptomatic hyperuricaemia condition is still controversial considering the benefit and side effects^[2]. Therefore, safe and effective anti-hyperuricemia therapies are necessary.

Objectives: Bergenin, the major bioactive ingredient isolated from *Saxifraga stolonifera*, could activate SIRT1. In this study, we identify the effect of bergenin on hyperuricemia, and explored the related mechanisms.

Methods: Significant hyperuricemia was established in C57BL/6N mice treated with oxonate and yeast polysaccharide. Bergenin was administered to the mice at the same time. The serum uric acid and creatinine levels, clearance of uric acid and creatinine, the intestinal uric acid excretion, and renal pathological lesions were determined were used to evaluate the anti-hyperuricemic effects. The location and expression levels of ABCG2 in the kidney and intestine were analyzed. HK-2 and Caco-2 cell lines were exposed to soluble uric acid with or without the treatment of Bergenin. Then the expression of ABCG2 and underlying mechanisms were explored.

Results: The administration of bergenin decreased serum uric acid in hyperuricemic mice by the promotion of uric acid excretion both in kidney and intestine. Bergenin rescued the downregulation of ABCG2 in the kidney of hyperuricemic mice and upregulated the expression of ABCG2 in the jejunum and ileum. In

vitro, Bergenin significantly increased the expression of ABCG2 as well as activated SIRT1, which was reversed by addition of PPAR γ antagonist GW9662 and siPPAR γ .

Conclusion: These findings suggest bergenin increases uric acid excretion both in the kidney and intestines, which may be related to the upregulation of ABCG2 via SIRT1-PPAR γ pathway.

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AB0054

SYNOVIAL CD163+ MACROPHAGES ARE ASSOCIATED WITH RADIOGRAPHIC JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS

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Background: CD163, a hemoglobin scavenger receptor, has been identified as a marker of M2 macrophages, it can promote the release of IL-10 and carbon oxide. Researches on inflammatory diseases and tumors have suggested that CD163 plays anti-inflammatory effect and promotes tumor growth and metastasis. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by chronic synovitis with inflammatory cells infiltration including considerable macrophages. However, little is known about the role of CD163+ macrophages in RA synovium.

Objectives: To investigate the expression and clinical significance of synovial CD163+ macrophages in RA.

Methods: Seventy-five RA patients were recruited and clinical data including disease activity, HAQ and Sharp/van der Heijde-modified Sharp score of bilateral hands and wrists were collected. Synovial tissues were obtained by needle biopsies or arthroscopy of knee joints. Eighteen osteoarthritis (OA) and seventeen orthopedic arthropathies (orth.A) patients were included as controls. All synovium were stained with H&E and immunohistochemically for CD163, CD3, CD20, CD38, CD68, and CD15. Histologic changes of synovitis in H&E stained sections were graded with Krenn's synovitis score.

Results:

1. Positive CD163 expression were found in both lining synoviocytes and sublining inflammatory cells. Both densities of lining and sublining CD163+ macrophages in RA synovium were significantly higher than that in OA or Orth.A synovium (140.47±66.93 vs. 17.85±7.70 vs. 19.76±5.26 and 417.92±249.62 vs. 27.58±14.19 vs. 29.87±9.33, all $P<0.001$, Figure 1).
2. According to Krenn's synovitis score, there were 68% RA patients showing high synovitis (score>4). Both lining and sublining synovial CD163+ macrophages were significantly higher than those showing low synovitis (lining: 158.40±62.91 vs. 122.06±66.74, sublining: 462.96±62.91 vs. 371.65±271.54, both $P<0.05$). Meanwhile, the densities of lining and sublining CD163+ macrophages were both positively correlated with Krenn's synovitis score ($r=0.238$ and 0.343 , both $P<0.05$).
3. For clinical relationship in RA, the density of sublining CD163+ macrophages was positively correlated with total Sharp score (mTSS) ($r=0.399$, $P<0.001$), joint space narrowing subscore ($r=0.248$, $P=0.032$) and joint erosion subscore ($r=0.457$, $P<0.001$). While the density of lining CD163+ macrophages was positively correlated with mTSS ($r=0.319$, $P=0.005$) and joint erosion subscore ($r=0.358$, $P=0.002$). Meanwhile, the densities of sublining and lining CD68+ macrophages were also positively correlated with mTSS ($r=0.253$ and 0.242 , both $P<0.05$), of which the correlation was weaker than that of CD163+ macrophages (Figure 2). There were no significant correlation between the density of CD163+ macrophages and disease activity or HAQ (all $P>0.05$).

Conclusion: Synovial CD163+ macrophages are associated with radiographic joint destruction, which imply that CD163+ macrophages may play role in the pathogenesis of joint destruction in RA.

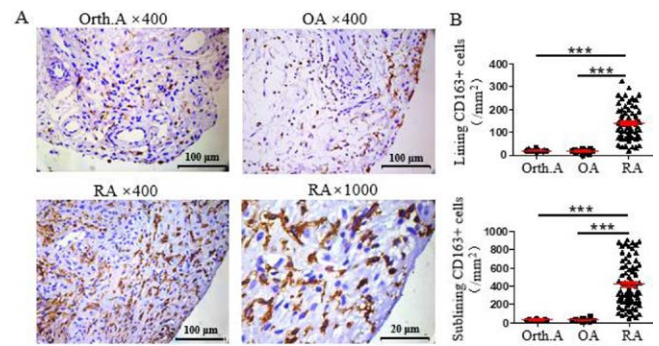


Figure 1. Representative immunohistochemical findings of synovial CD163 expression. (A) Synovial CD163 expression in an Orth.A patient, an OA patient and a RA patient. (B) Densities of lining and sublining CD163+ macrophages in Orth.A, OA and RA patients.

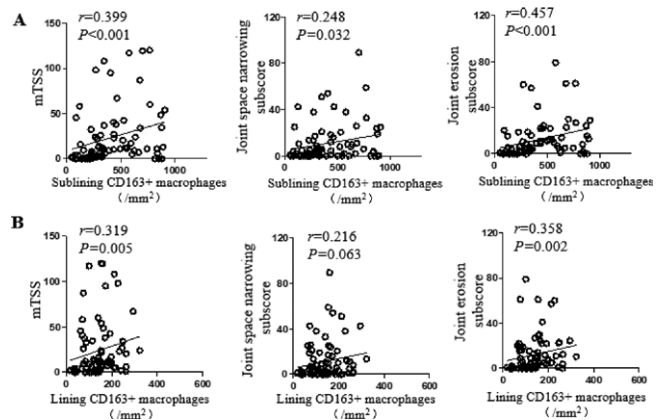


Figure 2. Spearman's rank correlation analysis for synovial macrophages and mTSS in RA. (A) Correlation between sublining CD163+ macrophages and mTSS, joint space narrowing subscore, joint erosion subscore. (B) Correlation between lining CD163+ macrophages and mTSS, joint space narrowing subscore, joint erosion subscore.

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Figures:

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AB0055

SOLUBLE TREM-1 LEVELS IN FAMILIAL MEDITERRANEAN FEVER RELATED AA-AMYLOIDOSIS

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Background: Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) is a monocyte and neutrophil receptor functioning in innate immunity. TREM-1 produces proinflammatory cytokines and serves for neutrophil degranulation. TREM-1 activity is well known in the pathogenesis of sepsis; hence it can be also present in autoinflammatory diseases such as the most common monogenic one, Familial Mediterranean Fever (FMF).

Objectives: The objective of this study is to measure soluble TREM-1 (sTREM-1) activity in severe FMF cases complicated with systemic AA-Amyloidosis.

Methods: The cohort of the study includes regularly followed FMF related AA-Amyloidosis patients in a tertiary center outpatient rheumatology clinic. Soluble TREM-1 levels were measured using enzyme-linked immunosorbent assay (ELISA). In addition, demographic data, renal function tests, acute phase reactants, and medical prescription history was also noted and analyzed. None of the FMF diagnosed patients had an attack during the collection of the blood samples.

Results: The patients were categorized into 4 groups: FMF related AA-Amyloidosis patients (A(+)) FMF(+)), FMF unrelated AA-Amyloidosis (FMF(-) A(+)),