Innate immunity in rheumatic diseases

AB0051 SERUM AMYLOID A AND PENTRAXIN 3: INNATE IMMUNE RESPONSE AND DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

R. Assandri[1], G. Martellosio[2], A. Montanelli[3]. [1] *ASST-Crema, Clinical Investigation Laboratory, Crema, Italy;* [2]*ASST-Brescia, Clinical Investigation Laboratory, Brescia, Italy;* [3]*ASST-Bergamo EST, Clinical Investigation Laboratory, Seriate, Italy*

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 2.8 ng/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, 6.5 mg/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 (PTX311.5 ± 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-kB.
References:
[1] Assandri R, Monari M Montanelli A. Pentraxin 3 in Systemic Lupus Erithematosus: Questions to be Resolved, Translational Biomedicine (2015)
Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2020-eular.1933

AB0052 ROLE OF TRAINED IMMUNITY AND IMMUNOMETABOLISM IN THE PATHOGENESIS OF ERDHEIM-CHESTER DISEASE

R. Biavasco[1], R. Molteni[1], D. Stefanoni[1], M. Ferrarini[2], E. Ferrero[2], S. Cenci[2], S. Cardaci[2], A. Boletta[2], L. Cassina[2], G. Di Stefano[2], J. Dominguez Andres[3], C. Doglioni[1], T. Nemkov[4], I. Merelli[2], A. D'alessandro[4], E. Montini[2], M. Netea[3], L. Dagna[1], G. Cavalli[1]. [1]*Vita-Salute San Raffaele University, Milan, Italy;* [2]*IRCCS San Raffaele Scientific Institute, Milan, Italy;* [3]*Radboud University Medical Centre, Nijmegen, Netherlands;* [4]*University of Colorado Denver, Aurora, CO, United States of America*

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.
Disclosure of Interests: Riccardo Biavasco Employee of: Bluebird, Raffaella Molteni: None declared, Davide Stefanoni: None declared, Marina Ferrarini: None declared, Elisabetta Ferrero: None declared, Simone Cenci: None declared, Simone Cardaci: None declared, Alessandra Boletta: None declared, Laura Cassina: None declared, Gianfranco Di Stefano: None declared, Jorge Dominguez Andres: None declared, Claudio Doglioni: None declared, Travis Nemkov: None declared, Ivan Merelli: None declared, Angelo D'Alessandro: None declared, Eugenio Montini: None declared, Mihai Netea: None declared, Lorenzo Dagna: None declared, Giulio Cavalli Consultant of: SOBI, Pfizer, Sanofi, Novartis, Paid instructor for: SOBI, Novartis, Speakers bureau: SOBI, Novartis
DOI: 10.1136/annrheumdis-2020-eular.2738

AB0053 BERGENIN, ACTING AS AN AGONIST OF SIRT1, REDUCE SERUM URATE IN MICE THROUGH THE UPREGULATION OF ABCG2

M. Chen[1], X. Lu[1], H. Wu[1]. [1]*Department of Rheumatology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China*

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 recued the downregulation of ABCG2 in the kidney of hyperuricemic mice and upregulated the expression of ABCG2 in the jejunum and ileum. In