AB0082  ANTI-INFLAMMATORY EFFECTS OF TOTAL SAPONINS OF PANAX JAPONICUS ON RHEUMATOID ARTHRITIS

J. Zhang1,2, X. Guo1,2, Q. Bu1,2, X. Shen1,2, Z. Feng1,2. Chinese Medicine Approved by State Administration of Traditional Chinese Medicine, Third-Grade Pharmacological Laboratory, Yichang, Hubei, China; 3China Three Gorges University, Medical College, Yichang, Hubei, China

Background: Rheumatoid arthritis (RA) is a common autoimmune disease with inflammation1. Total saponins of Panax japonicus (TSPJs) are effective components extracted from Panax japonicus. They are known to exhibit anti-inflammatory and immunosuppressive properties, but their effect of anti-inflammation in collagen-induced arthritis (CIA) remains unclear.

Objectives: To investigate the anti-inflammatory targets of TSPJ predicted by bioinformatics and the verification in CIA mice.

Methods: The targets of RA are obtained in the GeneCards database, we used Cytoscape 3.7.2 software to construct a protein-protein interactions (PPI) network and obtain the hub genes. There are four effective components of TSPJ: Araloside A, chikusetsusaponin Iva, ginsenoside Rg2, and ginsenoside Ro. Through molecular docking between the screened hub genes and the four effective components of TSPJ, the possibility of TSPJ treating CIA mice can be predicted. The collagen II (CII) and complete Freund’s adjuvant (CFA) were used to induce the CIA model. After establishing the model, 32 DBA1/J mice were divided into C group (n=8), M group (n=8), L group (n=8), and H group (n=8). The L and H groups were gavaged with TSPJ at 30mg/kg or 150mg/kg, and the C and M groups were gavaged with normal saline. The thickness of the hind paw, number of swollen joints, and arthritis index were evaluated. After 11 days of treatment, all the mice were sacrificed after anesthesia. Sera were collected to centrifuge tubes and the levels of inflammatory factor were determined by the ELISA kit following the instructions.

Results: A gene list that enriches 263 genes was obtained by searching RA from the GeneCards database. The hub genes of the top 3 obtained from Cytoscape 3.7.2 software were tumor necrosis factor (TNF), interleukin-1β (IL-1β), and interleukin-6 (IL-6). In addition, interleukin-17A (IL-17A), a classical inflammatory index in the top 10, was selected and included in the predicted target. The results of molecular docking between the predicted target and the components of TSPJ showed that the combined pose has good stability. The numerical value of hind paw thickness, swollen joint counts, and arthritis index in the intervention groups were lower than those in the M group, suggesting TSPJ played a critical role in treating CIA mice.

Conclusion: The current study demonstrated an effective effect of TSPJ on inflammatory inflammation in CIA mice, and TSPJ can act on the targets predicted by bioinformatics of CIA mice, suggesting the potential of TSPJ as a therapeutic agent for RA and providing new ideas for the clinical treatment of RA.

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AB0083  RELATIONSHIP BETWEEN APOPROTEIN C-III AND ACTIVATED FACTOR VII-ANTITHROMBIN COMPLEXES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PSORIASIC ARTHRITIS

A. Zielinska1, E. Zielinska1, J. Wróski1, J. Natorska2, A. Paradowska-Gorycka2, P. Gluszko2. 1National Institute of Geriatrics, Rheumatology and Rehabilitation, Rehabilitation, Warsaw, Poland; 2Institute of Cardiology, Jagiellonian University Medical College, Cardiac Surgery, Anesthesiology and Experimental Cardiology, Kraków, Poland; 3National Institute of Geriatrics, Rheumatology and Rehabilitation, Molecular Biology, Warsaw, Poland

Background: Both rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are associated with increased cardiovascular risk and thrombosis. Alterations in plasma lipids levels, including apolipoproteins are recognized as the important risk factors of cardiovascular disorders. Activated Factor VII-anti-Thrombin complex (FVIIa-AT) is a marker of the extrinsic coagulation cascade activation, the pathway accelerated by interaction with plasma apolipoprotein C-III (Apo-CIII) (1).

Objectives: To investigate the associations between plasma FVIIa-AT concentration, lipid profile including apolipoprotein CIII, and markers of disease activity in patients with RA and PsA.

Methods: 41 patients with RA, 38 with PsA, and 22 healthy controls, all not taking anticoagulant drugs were selected for the study. The lipid profile comprised triglycerides (TG), total cholesterol (TCh), low (LDL), and high density lipoprotein (HDL). Serum levels of Apo C-III were measured using a Human ApoCIII ELISA kit CellBiolabs Inc.Austria. FVIIa-AT plasma concentrations were determined using ELISA test. C-reactive protein (CRP) level was measured using the immuno-nutritrivometric assay. All measurements were performed by a technician blinded to sample origin. The Mann-Whitney test and Kruskal Wallis tests were applied for intergroup comparisons, and correlations were assessed using Spearman's rank tests, due to data non-normal distribution.

Results: The highest serum levels of Apo C-III were found in RA patients (median: 99.9/μg/ml, min.-max. 8.7–199) compared to PsA (30.86/μg/ml, 12.4–125.8) and controls (9.5 μg/ml, 3.7–29.2), p<0.001. RA and PsA patients revealed higher FVIIa-AT plasma levels than controls (RA median 153.8 pm, min.—max. 570–3978, PsA 157.6 pm, 64.9– 323.8 vs controls 104.5 pm, 68.9–150.9, p<0.001). In RA and PsA patients ApoCIII correlated positively with TG levels (r=0.35, p=0.027 and r=0.38, p=0.018 respectively). In all patients and controls, Apo C-III levels correlated positively with FVIIa-AT concentrations (r=0.45,p<0.001). No significant differences were found in the serum concentrations of TCh, LDL, HDL, and CRP, between the groups of RA and PsA patients.

Conclusion: Elevated concentrations of both, apolipoprotein CIII and activated FVIIa-AT complexes in rheumatoid patients suggest associations between plasma lipoproteins and activation of coagulation cascade leading to a pro-thrombotic state in patients with RA and PsA. Further studies on these relationships are necessary taking into account various clinical conditions of patients and treatment.

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AB0084  INCREASED LIVER DISEASE RISK IN RHEUMATOID ARTHRITIS IS ASSOCIATED WITH DISEASE ACTIVITY, INFLAMMATORY MARKERS, INSULIN RESISTANCE AND ACPAs. INFLUENCE OF METHOTREXATE

I. Arias de la Rosa1, M. Ruiz-Ponce1, L. Cuesta López1, M. Gahetse2, N. Herman-Sanchez3, A. Lucendo-Villarin4, P. Navarro-Sanchez4, M. C. Abalos-Aguilera2, C. Perez-Sanchez2, R. Ortega Castro4, J. Calvo Gutierrez5, C. Lopez-Pedrera2, A. Escudero Contreras6, E. Collantes Estevez7, N. Barbarroja Puerto8, 1Pitzer-University of Granada-Junta de Andalucia Centre for Genomics and Oncological Research, Genomic Medicine, Granada, Spain; 2IMIBIC/University of Cordoba/Reina Sofia Hospital, Rheumatology Department, Cordoba, Spain; 3University of Cordoba/IMIBIC/Reina Sofia Hospital, Cell Biology, Immunology and Physiology Department, Cordoba, Spain; 4Hospital General de Tomelloso, Gastroenterology Department, Cidad Real, Spain; 5University of Cordoba/IMIBIC/Reina Sofia Hospital, Medicine and surgical sciences, Cordoba, Spain

Background: Chronic inflammation, treatment with methotrexate (MTX) or even autoimmunity factors that might be involved, however the mechanisms related to this comorbidity in RA are not completely established yet.

Objectives: 1) To evaluate the liver disease risk in RA patients through feasible indexes to be used in the daily clinical practice and its relationship with clinical features of the disease; 2) To analyze the impact of antibodies to citrullinated proteins (ACPA) on MTX function; 3) To examine the influence of MTX treatment on clinical parameters and new indexes of hepatic dysfunction in a cross-sectional and longitudinal cohort.

Methods: 1) Cross-sectional study in 307 body mass index matched subjects: 55 healthy donors (HDs), 190 RA patients and 62 non-RA patients diagnosed with NALFD through echography. Obese patients were excluded from the study. 2) Longitudinal study with 50 RA patients treated with MTX for 6 months. Clinical and laboratory parameters, subclinical liver disease biomarkers and 4 indexes to evaluate the presence of fibrosis and steatosis (APRI, “AST to platelet ratio index”; FIB-4, “fibrosis 4 score”; HSI, “hepatic steatosis index” and TyG, “triglycerides and glucose index”) were measured. Association studies of hepatic dysfunction with clinical parameters were performed; A panel of 15 proteins directly involved in hepatic disease was analyzed in serum (C1QTNF1, IL7R, TIE1, CCL5, REG3A, CA3, LCN2, CCL14, NRP1, ICAM3, CD59, TIMP1, CNDP1, GNLY, IGFBB). 3) In vitro experiments were carried out in hepatocyte cell line (HEPG2) treated with ACPAs.

Results: Using NALFD patients as positive controls for the four liver disease indexes, RA patients showed significantly higher levels of HSI and TyG biomarkers. In fact, a high proportion of these patients (42.7%) were estimated to suffer NALFD. The association studies in RA patients showed that liver disease biomarkers (HSI and TyG) were related to the insulin resistance state, inflammation, complement component 3(C3), disease activity, and the levels of ACPAs. Serum levels of CNDP1, CCL5, GNLY, TIMP-1, CD59 and CCL14 were significantly increased in RA patients and correlated with hepatic damage indexes. Treatment with ACPAs on hepatocytes promoted the secretion of C3 in parallel with a significant alteration of genes related to glucose and lipid metabolisms, inflammation, fibrosis and apoptosis. MTX treatment, from the point of cross-sectional approach, was not associated with an increase of hepatic enzymes, serum proteins nor liver disease indexes. Treatment with MTX for 6 months did not affect those levels either.

Conclusion: 1) A high proportion of RA patients present an alteration in markers of NALFD, associated with insulin resistance state, disease activity, inflammation, complement component 3(C3), and ACPAs levels; 2) the autoantibodies could directly impact hepatocyte biology altering the expression of genes related to glucose and lipid metabolisms, inflammation, fibrosis and apoptosis. 3) Treatment with MTX did not promote any alteration in subclinical liver disease biomarkers after 6 months of treatment. Funded by Institute of Health Carlos III (PI20/00073).

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AB0086

TIGLYLCARNITINE AS KEY FACTORS IN LIVER–JOINT AXIS

H. Wang1, Y. Zhang1. 1Qilu Hospital, Department of Clinical Laboratory, Jinan, China

Background: Gut microbiota could promote RA progression metabolites mediated gut–joint axis [1]. We previously reported that liver metabolism has a close linkage with Rheumatoid arthritis (RA) [2]. However, the inter-relational mechanisms between liver and joint are still unclear.

Objectives: This article aimed to explore the shared metabolites signatures of liver, plasma and joint in RA.

Methods: We integrated multomics datasets metabolites of liver and plasma from the healthy group (n=10) and CIA group (n=10), and metabolites of knee-joint fluid (synovial fluid) from 40 participants in osteoarthritis (OA) group (n=20) and RA group (n=20). The Weighted Gene Co-Expression Network Analysis (WGCNA) was used to identify the co-expression modules related to liver, plasma and joint.

Results: The blue modules were negatively correlated with CIA (r = -0.74, p <0.001), included 200 liver metabolites. The black modules were positively correlated with CIA (r = 0.63, p <0.001), included 78 plasma metabolites. The yellow modules were positively correlated with RA (r = 0.53, p =0.008), included 55 synovial fluid metabolites. There were only 1 metabolite (Tiglylcarnitine) overlapped in RA-related module of liver, plasma and joint.

Conclusion: Tiglylcarnitine may be the key factors to liver–joint axis.

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