Conclusion: Increased OPN production by MSC can link mechanical load and new bone formation after the resolution of the inflammatory phase in axSpA.

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POS0042

HIGH-THROUGHPUT TRANSCRIPTOMIC PROFILING OF PERIPHERAL BLOOD MONONUCLEAR CELLS IN AXIAL SPONDYLOARTHRITIS PATIENTS REVEALS CO-EXPRESSED GENE MODULES ASSOCIATED WITH RADIOGRAPHIC DAMAGE

Methods:

Background: The use of high throughput techniques such as transcriptomic sequencing has recently made considerable progress in the identification of molecular profiles involved in the pathogenesis of chronic autoimmune diseases. To date, only a few studies have been carried out in axial spondyloarthriti (axSpA), which would allow the identification of new therapeutic targets and disease biomarkers.

Objectives: 1) To identify clusters of highly correlated genes enriched in biological functions and specific molecular pathways involved in the pathogenesis of axSpA. 2) To study the association between the molecular signatures identified and the clinical-analytical profile of the disease.

Methods: Cross-sectional study including 75 axSpA patients from the CAS-TRO cohort who underwent an exhaustive clinical evaluation including disease activity and functional limitation, structural damage, and spinal mobility. Additionally, analytical parameters were measured and the carotid intima-media thickness was evaluated by carotid eco-doppler. Mononuclear cells were purified from peripheral blood, and RNA was isolated. RNA from 25 axSpA patients was sequenced using the Illumina platform. For the identification of patient subgroups and the generation of co-expressed gene modules, the “hierarchical clustering” and WGCNA (“Weight gene correlation network analysis”) methodologies were used, respectively. Functional analysis of the genes conforming each module was carried out to identify enriched pathways through the UnichrR platform. Hub genes were measured through high throughput PCR (Fluidigm Biomark HD) in a validation cohort of 50 axSpA patients. Association and correlation studies between the molecular and clinical profiles were performed. In vitro studies in peripheral blood mononuclear cells (PBMCs) from patients belonging to different molecular clusters were performed.

Results: Unsupervised analysis of the transcriptome revealed the presence of two “clusters” of axSpA patients, clearly differentiated by their molecular and clinical profiles. Specifically, the molecular analysis distinguished patients with longer disease duration, greater disease activity, radiographic damage, and cardiovascular risk. WGCNA identified 11 highly co-expressed modules. Among them, six were differentially expressed between the two clusters, being responsible for the molecular and clinical distinction of those groups. The functional analysis of these 6 gene modules revealed the enrichment of these genes in pathways related to inflammation, oxidative metabolism, proliferation of B and T lymphocytes, immune response, and the increase of cell survival. Finally, key genes were identified within each module (“hub genes”), whose expression was associated with a more active phenotype of the disease such as ALOX5, GAB2, PSMD13, CASP8, NOTCH e ITGA4. Hub genes were validated in an additional cohort of 50 axSpA patients and correlated with mSASSS. Treatment of PBMCs from patients belonging to the two different clusters with autologous serum induced a different expression of genes involved in cell activation and inflammation.

Conclusion: The whole transcriptomic analysis by RNAseq in peripheral mononuclear cells from axSpA patients distinguished, in an unsupervised manner, subgroups of patients with distinctive clinical profiles. The analysis of gene modules identified new pathways and molecular functions potentially involved in the pathophysiology of the disease. Funded by ICSII (PMP21/00119) co-financed by ERDF, Andalusian Foundation of Rheumatology (FAR).

References: [1]

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POS0043

COMPLEMENT IN RADIOGRAPHIC AXSPA – BIOMARKERS OF RADIOGRAPHIC PROGRESSION? POST HOC ANALYSIS FROM CONSUL, A LONGITUDINAL MULTI-CENTER RANDOMIZED CONTROLLED TRIAL COHORT OF AXSPA-PATIENTS WITH A HIGH RISK OF STRUCTURAL PROGRESSION INITIATING TREATMENT WITH TNF-I

Keywords: Innate immunity, bDMARD, Spondyloarthritis

Methods:

Background: The biological processes involved in the development of structural changes associated with radiographic axial spondyloarthritis (r-axSpA) remain largely unsolved. Still, high disease activity, elevated C-reactive protein (CRP), and existing syndesmophytes are associated with radiographic progression. The complement system is an inflammation-generating part of the innate immune system. Animal models have shown inhibition of complement activation to diminish structural changes associated with axSpA [1].

Objectives: This project aimed to investigate complement activation and serum levels of complement components and their correlations with radiographic spinal progression over a two years follow-up period in a longitudinal cohort of axSpA patients with active r-axSpA, and high risk of radiographic progression, recruited from the randomized controlled trial CONSUL.

Methods: All patients had active r-axSpA and risk factors for radiographic spinal progression (BASDAI >4, and elevated CRP and/or or >1 syndesmophyte(s)). Serum samples were collected at baseline (n = 96) and after 108 weeks (n = 74) of TNF-I therapy and analyzed by immunoassays for complement lectin pathway proteins (L-ficolin, M-ficolin, H-ficolin, CL-L1, MBL, MASP-1, MASP-2, MASP-3, and MAp44) and the complement activation product C3dg. X-rays were performed at baseline and after 108 weeks and read blinded for clinical data and chronology by three independent expert readers. New bone formation was defined as the growth of syndesmophyte(s) and/or new syndesmophyte(s) determined by 3-reader-agreement.

Results: Patient characteristics are shown in Table 1. In total, 19 patients developed new bone formation at week 108. Baseline serum levels of MASP-1, MASP-2, and C3dg were elevated in patients with new bone formation, whereas baseline serum levels of MASP-3 were decreased (p<0.05). Baseline MASP-1, MASP-3, and C3dg predicted the development of new bone formation in a univariate logistic regression analysis, whereas CRP did not. Baseline MASP-1, MASP-3, and C3dg remained significant in a multivariate logistic regression analysis, L-ficolin and C3dg levels at week 108 were elevated in patients with new bone formation, and the serum levels at week 108 predicted development of new bone formation in a univariate logistic regression analysis. In a multivariate logistic regression analysis, C3dg remained significant (p<0.05).

Conclusion: In this study, complement activation measured by C3dg and serum levels of MASP-1 and MASP-3, prior to TNF-I therapy, predicted development of new bone formation at week 108. Furthermore, elevated levels of C3dg and L-ficolin at week 108 were associated with new bone formation. These findings support the involvement of complement activation in new bone formation in r-axSpA.

References: