shown that the largest factor influencing disease susceptibility is genetics. Genome-wide association studies have successfully characterized genetic variants that are associated with RA, with the vast majority of them mapping to non-coding regulatory elements. Understanding the mechanisms by which this phenomenon leads to disease is essential to translate results from genetic association studies to the clinic.

Objectives: There is evidence showing that autoimmune diseases are the consequence of erroneous wiring of the regulatory circuitry between enhancers and their target genes. The aim of this study is to characterize non-coding regions containing RA-associated variants, in order to determine the genes and pathways by which these regions act to increase the risk of disease.

Methods: We isolated CD4+ T-cells from blood obtained from RA patients. We stratified patients in two subgroups, high disease activity (DAS28>5.1) and low disease activity (DAS28<3.2, n=33). All samples were genotyped using Illumina Infinium Exome-24 v1.0 BeadChip arrays. RNA-Seq Libraries were generated for matching RNA samples using the Lexogen QuantSeq Library Prep kit and sequenced on an Illumina NextSeq500. For a subset of 6 samples (3 high disease activity and 3 low disease activity patients), capture Hi-C was performed to characterize chromatin interactions between all RA associated loci and their potential target genes.

Results: We observed numerous chromatin interactions between RA variants and potential causal genes. Preliminary results show that a number of disease-associated SNPs interact with compelling candidate genes situated several megabases away. Whilst some of these chromatin interactions are common to both patients groups, subsets of them are specific to each disease subgroup, which are correlated with differential gene expression.

Conclusion: These results suggest that there might be different biological pathways contributing to disease in RA patients with inactive disease compared to patients with high disease activity.

Disclosure of Interests: None declared.


**FR01006**

**PROTECTIVE ROLE OF THE PROPROPTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) RS2495477 POLYMORPHISM IN PATIENTS WITH RHEUMATOID ARTHRITIS AND SUBCLINICAL Atherosclerosis**

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**Background:** RA is associated with the development of cardiovascular (CV) disease and subclinical atherosclerosis. The presence of carotid plaques assessed by ultrasonography studies is a surrogate marker for subclinical atherosclerosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is involved in homeostasis of cholesterol, a traditional CV risk factor related to RA and atherosclerosis. PCSK9 polymorphisms can both increase and decrease the risk of CV disease in patients with atherosclerosis. Moreover, PCSK9 levels have been also related with CV risk. However, there is little information on PCSK9 in RA.

**Objectives:** To assess the role of several PCSK9 polymorphisms in RA and subclinical atherosclerosis in RA as well as to determine if these genes may influence the levels of PCSK9 mRNA and protein levels.

**Methods:** PCSK9 rs2479409, rs11583680, rs2483205, rs2495477 and rs6525565 polymorphisms were genotyped in 1,169 Spanish RA patients, who met the 1987 ACR and the 2010 ACR/EULAR criteria for RA, and 528 healthy controls. Associations were estimated using odds ratios (OR) and 95% confidence intervals (CI). The potential association between PCSK9 polymorphisms and both RA risk and controls and the presence-absence of carotid plaques in RA was evaluated by logistic regression.

**RESULTS:** PCSK9 mRNA expression and PCSK9 serum levels were determined by qPCR and ELISA, respectively. All results were adjusted by sex, age and traditional CV risk factors.

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**FR01007**

**IDENTIFICATION AND VALIDATION OF PLASMA MICRORNA 425–5P AND 451A AS MICRO-RNAS ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK OBSERVED IN RHEUMATOID ARTHRITIS PATIENTS**

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**Background:** Cardiovascular disease (CVD) risk is increased in rheumatoid arthritis (RA) patients, and therefore, improved approaches for its early detection are needed. An accelerated atherosclerosis is considered the cause of the increase CVD risk. As microRNAs (miRNAs) are increasingly recognized as critical regulators in atherosclerosis and possess excellent stability in plasma, this study focused on using miRNAs as noninvasive CVD risk biomarkers in RA patients.

**Objectives:** To identify plasmatic miRNAs in RA patients that can facilitate earlier diagnosis of CVD and provide insight regarding the increase risk for CVD observed in these patients.

**Methods:** A discovery and validation studies were performed. To discover miRNAs candidates, we first compared plasmatic profiles of 754 miRNAs in 7 RA patients without CVD, in 7 patients with acute myocardial infarction (AMI) but without RA, and in 7 healthy controls matched for age and for classical CVD risk factors. miRNAs commonly expressed in the two group of patients but differentially expressed from the controls were selected as miRNA candidates for validation. Selected miRNAs were validated in independent serum samples from 214 RA patients (validation cohort) by studying its association with subclinical atherosclerosis measured by carotid intima-media thickness (cIMT). Plasma profile of miRNAs in the discovery study was analyzed using validated TaqMan Open Array miRNA panels which enables the quantification of 754 human miRNAs.
Differential expression analysis was performed with Expression Suite software and selected miRNAs candidates were validated in the validation study by qPCR. miRNA microarray data and different algorithms were used for statistical analysis.

**Results:** In the discovery study we were able to measure 379 (50%) of the miRNAs represented in the array. We observed 10 miRNAs (miRNA-Let-7a, miRNA-96, miRNA-381, miRNA-451a, miRNA-518d, miRNA-425-5p, miRNA-199b, miRNA-708, and miRNA-1180) that were expressed at the same level in RA and AMI patients but were significantly downregulated compared with controls. These 10 miRNAs were selected as potentially miRNAs associated with the increase risk of CVD in RA patients. Four of those miRNAs were expressed at very low level and were discarded for the validation study. In the validation study with 214 plasma samples of RA patients, we observed that two of the six candidate miRNAs (miRNA-425-5p and miRNA-451a) were significantly correlated with cIMT. Thus, adjusted multivariable linear regression analysis showed that miRNA-425-5p and miRNA-451a independently explained 1.4% of the cIMT variability. Furthermore, adjusted regression estimates of the effect of miRNA-425-5p and miRNA-451a on cIMT were \( \beta = 0.029 \text{mm} \), \( p = 0.004 \) and \( \beta = 0.030 \text{mm} \), \( p = 0.009 \), respectively. No other miRNA candidate exhibited association with cIMT values. Furthermore, we observed that miRNA-425-5p was significantly correlated with ESR (\( r = 0.136 \); \( p = 0.024 \)) and miRNA-451a with DAS28 (\( r = 0.19 \); \( p = 0.003 \)).

**Conclusion:** In the present study, we have identified miRNA-425-5p and miRNA-451 as potentially miRNAs involved in the CVD risk observed in RA patients.

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