Objectives: To explore potential mechanisms for the SLE related IRF7 SNP on type I IFN production, which might indicate new theoretical basis for genetic therapeutic strategy.

Methods: We constructed different genotypes of SLE relevant SNP cell lines by Crispr/Cas9 technology, and confirmed them by sequencing. After TLR-ligand stimulation, the mRNA expression of IFN α was detected by real-time qPCR. The levels of IFN α , TNF α and IL-6 were detected by ELISA kit. The protein expression of IRF7/p-IRF7 was detected by western blot. The binding ability of endogenous IRF7 with type I IFN promoter was studied by chromatin immunoprecipitation.

Results: We got IRF7 SNP rs1131665 GG/AA cell lines by gene editing technique. After TLR-ligand stimulation, IRF7 SNP rs1131665 AA cell line showed higher IFN α expression than GG, which indicated statistical significance. IRF7 SNP rs1131665 AA cell line showed higher p-IRF7 expression than GG detected with western blot. Endogenous IRF7 in IRF7 SNP rs1131665 AA cell line showed stronger binding ability with IFN α promoter than GG, which indicated statistical significance.

Conclusion: The missense variant of G to A in IRF7 SNP rs1131665, increased the production of type I IFN, which indicated that IRF7 G to A missense variant increased the susceptibility of type I IFN associated diseases.

REFERENCES:

- Lin LH, Ling P, Liu MF. The potential role of interferon-regulatory factor 7 among Taiwanese patients with systemic lupus erythematosus. *J Rheumatol*. 2011;38(9):1914-1919.
- Xu WD, Zhang YJ, Xu K, et al. IRF7, a functional factor associates with systemic lupus erythematosus. *Cytokine*. 2012;58(3):317-320.
- Miyagawa F, Tagaya Y, Ozato K, et al. Essential Requirement for IFN Regulatory Factor 7 in Autoantibody Production but Not Development of Nephritis in Murine Lupus. *J Immunol*. 2016;197(6):2167-2176.

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FRI0004

CHROMATIN INTERACTIONS IN NOVEL CELL TYPES REVEAL PARK7 AND ERFF1 AS PUTATIVE CAUSAL GENES IN THE SUSCEPTIBILITY TO PSORIATIC ARTHRITIS

Oliver Gough¹, Helen Ray-Jones², Paul Martin¹, John Bowes¹, Antony Adamson³, Anne Barton¹, Richard B. Warren⁴, Stephen Eyre¹. ¹Versus Arthritis Centre for Genetics and Genomics, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, United Kingdom, Manchester, United Kingdom; ²NIHR Manchester Biomedical research Centre, Manchester University Foundation Trust., Manchester, United Kingdom; ³Faculty of Biology, Medicine and Health University of Manchester, Manchester, United Kingdom; ⁴Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester, United Kingdom

Background: One of the major tasks post-GWAS is to link disease associated single nucleotide polymorphisms (SNPs) to their causal genes. Unexpectedly the vast majority of disease associated SNPs lay outside protein coding regions of the genome, often in gene regulatory regions, known as enhancers. These enhancers operate by physically interacting with their target genes, often over long distance, and often skipping genes. We, and others, have demonstrated how these enhancer interactions can change with different cell type and stimulatory conditions. In psoriatic arthritis, as with all complex diseases, there are a large number of genetic loci implicated in susceptibility to disease, but relatively few of these regions have confirmed causal genes.

Objectives: Map disease associated enhancers to potential causal genes through physical chromatin interactions in relevant, novel cell types.

Methods: We used Capture HiC (CHI-C) technology to map enhancer to promoter interactions in both a keratinocyte cell line (HaCaT) and a T cell line (MyLa) in biological duplicate. We generated Hi-C libraries and enriched them for autoimmune-associated GWAS loci using RNA baits. The resultant CHI-C libraries underwent high-throughput sequencing generating 75 bp paired-ends. Significant interactions were detected using CHiCAGO.

Results: A region on chromosome 1p36 demonstrated markedly differential interactions between the T cell line (MyLa) and the skin cell line (HaCaT). Here the enhancer region containing SNPs associated with PsA demonstrated a strong interaction with both the PARK7 and ERFF1 genes in HaCaT cells, absent in the MyLa cell line (fig 1). These interactions were contained within a functionally relevant topological activation domain (TAD) boundary, enriched for enhancer to promoter links. Bioinformatic

analysis demonstrated how a SNP highly correlated with the PsA lead variant is found within an open, active region of chromatin in the HaCaT cell line, shifting the priority from the (statistical) lead variant (rs11121129) to rs11121131 – demonstrating the value of this type of analysis (fig 2).

Conclusion: A region associated with PsA on chromosome 1p36, previously annotated with the TNFSF9/ERRF1/SLC45A1 gene, makes robust interactions with the PARK7 and ERFF1 genes, both strong candidates for causality in disease. An associated variant, within a cell type relevant enhancer, is currently being targeted with genome editing technology (CRISPR) to assess its potential for causality and possible mechanism.

Fig1

Fig2

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FRI0005

CHROMATIN CONTACTS AND TRANSCRIPTOMICS IN CD4+ T-CELLS REVEAL GENES IMPLICATED IN RHEUMATOID ARTHRITIS

Vasanthi Priyadarshini Gaddi¹, Amanda McGovern¹, James Ding¹, Nadia Iqbal¹, Chenfu Shi¹, Theoni Katopodi¹, Marialbert Acosta-Herrera², Sofia Vargas², Kate Duffus¹, Annie Yarwood¹, Enrique Raya³, Javier Martin Ibanez², Paul Martin¹, Gisela Orozco¹. ¹University of Manchester, Manchester, United Kingdom; ²Instituto de Parasitología y Biomedicina López-Neyra, CSIC, Granada, Spain; ³Hospital Clínico de Granada, Department of Rheumatology, Granada, Spain

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of synovial joints. RA is a clinically heterogeneous disease and treatment response varies between individuals. The pathogenesis of RA is not completely understood yet, but it has been

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, n=18) 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 suggests that there might be different biological pathways contributing to disease in RA patients with inactive disease compared to patients with high disease activity.

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FRI0006

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

Sara Remuzgo-Martínez¹, Fernanda Genre¹, Verónica Pulito-Cueto¹, Alfonso Corrales¹, Javier Llorca², Verónica Mijares¹, Leticia Lera-Gómez¹, Virginia Portilla¹, Iván Ferraz-Amaro³, Santos Castañeda⁴, Oreste Gualillo⁵, Javier Martín Ibanez⁶, Ricardo Blanco¹, Raquel López-Mejías¹, Miguel A. González-Gay^{1,7}. ¹Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Santander, Spain; ²Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain; ³Division of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain; ⁴Rheumatology Department, Hospital Universitario de La Princesa, IIS-IPrincesa, Madrid, Spain; ⁵SERGAS (Servizo Galego de Saude) and IDIS (Instituto de Investigación Sanitaria de Santiago), The NEIRID Group (Neuroendocrine Interactions in Rheumatology and Inflammatory Diseases), Santiago University Clinical Hospital, Santiago de Compostela, Spain; ⁶Instituto de Parasitología y Biomedicina "López-Neyra", CSIC, PTS Granada, Granada, Spain; ⁷School of Medicine, University of Cantabria, Santander, Spain

Background: RA is associated with the development of cardiovascular (CV) disease and subclinical atherosclerosis¹. The presence of carotid plaques assessed by ultrasonography studies is a surrogate marker for subclinical atherosclerosis². Proprotein convertase subtilisin/kexin type 9 (PCSK9) is involved in homeostasis of cholesterol, a traditional CV risk factor related to RA and atherosclerosis^{1,3}. PCSK9 polymorphisms can both increase and decrease the risk of CV disease in patients with atherosclerosis³. Moreover, PCSK9 levels have been also related with CV risk⁴. 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 ones may influence on PCSK9 mRNA and protein levels.

Methods: PCSK9 rs2479409, rs11583680, rs2483205, rs2495477 and rs562556 polymorphisms were genotyped in 1,169 Spanish RA patients, who met the 1987 ACR and the 2010 ACR/EULAR criteria for RA⁵⁻⁶, and 528 healthy controls. Associations were estimated using odds ratios (OR) and 95% confidence intervals (CI). The potential association between PCSK9 polymorphisms in both RA and controls and the presence/absence of carotid plaques in RA was evaluated by logistic regression. 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.

Results: Significant differences in the allele frequencies of PCSK9 rs2495477 between RA patients and controls were found (minor allele: OR=0.55, 95% CI=0.34-0.89, p=0.01). A significant association between minor allele of rs2495477 and carotid plaques was also disclosed in RA patients (OR=0.72, 95% CI=0.56-0.92, p=0.01). PCSK9 levels were significantly decreased in RA patients carrying rs2495477 minor allele compared to controls (97.8 ± 104.9 vs 235.8 ± 93.5 ng/mL, p=0.001). None of the five PCSK9 polymorphisms influenced on its expression.

Conclusion: Our study showed for the first time that PCSK9 rs2495477 confers protection against RA susceptibility and the development of sub-clinical atherosclerosis in RA patients. Furthermore, rs2495477 decreased PCSK9 serum levels in RA that may be crucial to control the disease.

REFERENCES:

- [1] Autoimmun Rev. 2016; 15: 1013–30.
- [2] Ann Rheum Dis. 2014; 73: 722–7.
- [3] J Am Coll Cardiol. 2005; 45: 1611–9.
- [4] Atherosclerosis. 2016; 252: 50–60.
- [5] Arthritis Rheum. 1988; 31: 315–24.
- [6] Arthritis Rheum. 2010; 62: 2569–81.

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FRI0007

IDENTIFICATION AND VALIDATION OF PLASMA MICRO-RNA 425-5P AND -451A AS MICRO-RNAs ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK OBSERVED IN RHEUMATOID ARTHRITIS PATIENTS

PARADES SILVIA¹, Delia Taverner², Raimon Ferre³, Josep Maria Alegret⁴, Lluís Masana⁵, Joan Carles Vallve⁵. ¹Hospital Universitari Sant Joan, Department of Rheumatology, Reus, Spain; ²Hospital Universitari Sant Joan, Department of Rheumatology, Reus, Spain; ³Hospital Universitari Sant Joan, Internal Medicine, Reus, Spain; ⁴Hospital Universitari Sant Joan, Department of Cardiology, Reus, Spain; ⁵Rovira i Virgili University, Lipid Research Unit, Reus, Spain

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 CV 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.