Background: Early diagnosis of axial Spondyloarthritis (axSpA) represents a major clinical challenge nowadays. Increasing evidence has determined that early diagnosis, prompt treatment initiation and early achievement of remission are the best predictors of long-term clinical, functional and radiographic outcomes. New tools to support the diagnosis are needed.

Objectives: This study aims to identify differentially expressed genes that may improve the current clinical diagnosis approach for early axSpA.

Methods: A cross-sectional study was conducted on 50 participants, 25 patients with axSpA (according to ASAS criteria) and 25 Healthy Controls, matched by age, gender, smoking status, and glucocorticoid use. Gene Set Enrichment Analysis (GSEA) was used to identify significant pathways associated with cell composition, smoking status, and glucocorticoid use. Gene Set Enrichment analysis using Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) annotations were also performed. A number of Differently Expressed Genes were highlighted.

Results: 311 genes were identified as being significantly differentially expressed between patients and controls. In details, 129 downregulated (7 genes have fold change more than 1) and 182 upregulated genes (3 genes have fold change more than 1) are highlighted. These genes are mostly involved in Myogenesis, Innate Immune Signalling and JAK/STAT pathways. Several genes with functions of skeletal muscle development and muscle contraction were identified.

Conclusion: The evidence disclosed that regulation of muscle development and contraction may be also engaged in physiopathology mechanisms of axSpA. These new cues open new perspectives for diagnosis and therapeutic approaches in axSpA.

Acknowledgments: To all patients and healthy people who participate in MySpA study

Disclosure of Interests: Atlas Mashayekhi Sardoe: None declared, Daniel Sobral: None declared, Lucia Domingues: None declared, Santiago Rodriguez-Manica Speakers bureau: Jansse, MSD, Novartis, Ritsa Pinheiro Torres: None declared, Agna Neto: None declared, Patricia Alves: None declared, Julia Costa: None declared, Nair declared, Jairnano declared, Jairnana declared, Jairnara declared, Jairnara declared, Jairnara declared.

THU0022

DIFFERENTIAL DNA METHYLATION AS A PREDICTOR OF TOCILIZUMAB RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Tocilizumab (TCZ) is a biological disease-modifying antirheumatic drug that blocks IL-6 signalling and is effective in ameliorating disease activity in rheumatoid arthritis (RA). However, approximately 50% of patients do not respond adequately to TCZ and some patients report adverse events. Considering there is growing evidence that DNA methylation is implicated in RA susceptibility and response to some biologics (1, 2), we investigated DNA methylation as a candidate biomarker for response to TCZ in RA.

Objectives: To identify differential DNA methylation signatures in whole blood associated with TCZ response in patients with RA.

Methods: Epigenome-wide DNA methylation patterns were measured using the Infinium EPIC BeadChip (Illumina) in whole blood-derived DNA samples from patients with RA. DNA was extracted from blood samples taken pre-treatment and followed by therapy. Analysis was performed at 0 months using the Clinical Disease Activity Index (CDAI). Patients who had good response (n=10) or poor response (n=10) to TCZ by 6 months were selected. Samples from secondary poor responders (n=10) patients who had an improvement of CDAI and were in remission at 3 months, followed by a worsening of CDAI at 6 months) were also analysed. Differentially methylated positions and regions (DMPs/DMRs) were identified using linear regression, adjusting for gender, age, cell composition, smoking status, and glucocorticoid use. Gene Set Enrichment Analysis (GSEA) was used to identify significant pathways associated with response and Functional Epigenetic Module analysis of interactome hotspots in regions of differential methylation.

Results: 20 DMPs were significantly associated with response status at 6 months in the pre-treatment samples. Another 21 DMPs were associated with response in the 3 month samples. Within good responders, 10 DMPs showed significant change in methylation level between pre-treatment and the 3 month samples (unadjusted P-value <0.05). One DMP, cg03121467, was significantly less methylated in good responders compared to poor responders in the pre-treatment samples. This DMP is close to EPB41L4A and thought to have a role in β-catenin signalling. GSEA of DMRs in non- and secondary non- responders identified histone acetyltransferase pathways and included the KAT7A gene, which is a repressor of NF-κB. Additional analysis of interaction hotspots of differential methylation identified significant interactions with STABMP and PTPN12 associated with response status.

Conclusion: These preliminary results provide evidence that DNA methylation patterns may predict response to TCZ. Validation of these findings in other larger data sets is required.

References:


Disclosure of Interests: Nisha Nair: None declared, Darren Plant: None declared, John Isaacs Consultant of: AbbVie, Bristol-Myers Squibb, Eli Lilly, Gilead, Janssen, Merck, Pfizer, Roche, Ann Morgan Grant/research support from: I have received a grant from Roche Products Ltd to establish a registry for GCA patients treated with tocilizumab., Consultant of: I have undertaken consultancy work for Roche, Chugai, Regeneron, Sanofi and GSK in the area of GCA therapeutics., Speakers bureau: I have presented on tocilizumab therapy for GCA and glucocorticoid toxicity on behalf of Roche products ltd., Kimme Hyrich Grant/research support from: Pfizer, UCBB, BMS, Speakers bureau: Abbvie, Annie Barton Consultant of: AbbVie, Anthony G Wilson: None declared.

DOI: 10.1136/annrheumdis-2020-eular.4394
Results: Among the 117 patients with RP, 5 (4.3%) and 6 (5.1%) patients had GD and HT, respectively. Patients with RP were more likely to be complicated with GD (p=1.04x10^-3), OR: 7.15, 95%CI 2.68-18.14) but not with HT (p=0.50, 95%CI 0.59-1.27), compared with prevalence in general Japanese population (0.62% and 5.9%, respectively). RP patients with GD showed a trend to have nasal involvement (100% vs 45.5%, p=0.023, OR: 2.58, 95%CI 1.09-9.84). We did not observe any differences in clinical manifestation in patients with RP and HT. HLA-DPB1*02:02 demonstrated a trend toward GD complication (20% vs 2.3%, p=0.035, OR: 10.41, 95%CI 1.23-65.38). There were no association of HLA in the complication of HT among patients with RP.

Conclusion: Patients with RP have high co-occurrence ratio of GD. Patients with the two diseases may be characterized by nasal involvement and HLA-DPB1*02:02.


Disclosure of Interests: Toshiaki Nakajima Speakers bureau: Bristol-Myers Squibb and Novartis, Hajime Yoshifuji Grant/research support from: Astellas Pharma. (Outside the field of the present study.), Speakers bureau: Chugai Pharmaceutical. (Outside the field of the present study.), Yoshitsuka Yamanoue: None declared, Hiroshi Handa: None declared, Koshirou Ohmura Grant/research support from: Astellas Pharma, AYUMI Pharmaceutical, Chugai Pharmaceutical, Daichi Sankyo, Eisai, Japan Blood Products Organization, Mitsubishi Tanabe Pharma, Nippon Kayaku, Nippon Shinyaku, Sanofi, and Takeda Pharmaceutical., Speakers bureau: AbboVie, Astelion Pharmaceuticals Japan, Asahi Kasei Pharma, AYUMI Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis Pharma, and Sanofi., Tsuneyo Mimori: None declared, Chikashi Terao Grant/research support from: Actelion, Speakers bureau: Asteras, Asahi Kasei Pharma, Ono and Tanabe-Mitsubishi.

DOI: 10.1136/annrheumdis-2020-eular.5349

THU0024 METHYLATION ANALYSIS OF VITAMIN D SIGNALING PATHWAY GENES IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Vitamin D is known for its immunomodulatory and epigenome interacting effects. Vitamin D deficiency is frequently observed in rheumatoid arthritis (RA) patients compared to healthy controls, is also named as a potential risk factor in RA ethiopathogenesis and may alter DNA methylation of certain genes [1,2]. Still, causality of vitamin D deficiency in RA patients needs to be elucidated.

Objectives: The aim of the study was to evaluate relationship between DNA methylation status of vitamin D related genes (VDR, CYP24A1, CYP2R1, miRNA-155) expression, vitamin D level and its association with RA.

Methods: 35 miRNAs and 34 RNA targets were identified. Expression of miRNA-155 in a miRNA expression panel was determined by qPCR. miRNA expression was used as an indicator of the target gene expression levels. CYP24A1 and CYP2R1 were analyzed in cell lines and RNA from blood samples. QTL2 sequencing was used to determine variant T3'UTR sequences. The data was analyzed using the Student's t-test.

Results: Among the 35 miRNAs, CYP24A1 and CYP2R1 showed a significant correlation with miRNA-155 expression. The expression of CYP24A1 and CYP2R1 in healthy controls was significantly lower than in RA patients (p<0.05). The expression of miRNA-155 was also lower in RA patients compared to healthy controls (p<0.05). The expression of CYP24A1 and CYP2R1 was also significantly lower in RA patients compared to healthy controls (p<0.05).

Conclusion: Vitamin D plays a role in the ethiopathogenesis of RA and its deficiency may alter DNA methylation of certain genes. The data of our study suggests that epigenetic phenomena are significantly involved in vitamin D metabolism and may have an indirect effect on RA ethiopathogenesis.


Disclosure of Interests: Toshiaki Nakajima Speakers bureau: Bristol-Myers Squibb and Novartis, Hajime Yoshifuji Grant/research support from: Astellas Pharma. (Outside the field of the present study.), Speakers bureau: Chugai Pharmaceutical. (Outside the field of the present study.), Yoshitsuka Yamanoue: None declared, Hiroshi Handa: None declared, Koshirou Ohmura Grant/research support from: Astellas Pharma, AYUMI Pharmaceutical, Chugai Pharmaceutical, Daichi Sankyo, Eisai, Japan Blood Products Organization, Mitsubishi Tanabe Pharma, Nippon Kayaku, Nippon Shinyaku, Sanofi, and Takeda Pharmaceutical., Speakers bureau: AbboVie, Astelion Pharmaceuticals Japan, Asahi Kasei Pharma, AYUMI Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis Pharma, and Sanofi., Tsuneyo Mimori: None declared, Chikashi Terao Grant/research support from: Actelion, Speakers bureau: Asteras, Asahi Kasei Pharma, Ono and Tanabe-Mitsubishi.

DOI: 10.1136/annrheumdis-2020-eular.5349