Background: Systemic sclerosis, a rare chronic inflammatory disease, is characterized by immune system activation, vasculopathy, and fibrosis of the body organs. Emerging evidence have so far indicated that autoantibodies (abs) directed against G protein-coupled receptors (GPCRs) particularly contribute to the SSc pathogenesis and induce the release of inflammatory and profibrotic proteins by immune cells such as monocytes [1-3]. Increased levels of autoantibodies against the angiotensin II type 1 receptor (AT1R abs) have been found in SSc patients [4-5], which are associated with increased secretion of extracellular vesicles (EVs) [6]. Interestingly, upregulated CCL18 levels could be associated with AT1R-EVs in SSc patients [7]. EVs play an important role in the pathogenesis of diseases by packing and transfer of AT1R to different tissues and immune cells, exemplary shown by activated cardiomyocytes leading to higher responsiveness to angiotensin II of recipient cells and vessels [9]. Taken together, the importance of studying anti-GPCR-abs together with GPCR-EVs in the pathogenesis of SSc becomes evident [10].

Objectives: Here we decipher the immune response of peripheral blood monocytes mediated by anti-AT1R-abs and EVs, in the pathogenesis of SSc.

Methods: Monoclonal AT1R ab (AT1R mab) has been generated by hybridoma technique, sequenced and recombinantly expressed in HEK cells. Human peripheral blood monocytes and mononuclear cell lines were stimulated by the recombinant monoclonal anti-human AT1R ab and, in comparison, in the presence or absence of EVs precipitated from sera of SSc patients versus sera of HD. The response of the monocytes was measured via CCL18 secretion by ELISA.

Results: We compared CCL18 release, a profibrotic cytokine, of mononucletic cells upon stimulation for 24h with the AT1R ab in presence or absence of sera EVs (SSc vs. HD). The recombinant monoclonal anti-human AT1R antibody induced secretion of CCL18 by monocytes. Our data indicate that EVs together with AT1R mab have an effect on monocyte activation and CCL18 secretion. Remarkably, combination of SSc-EVs, but not of HD-EVs, with the recombinant AT1R mab showed an additive effect on monocyte activation and CCL18 response (Figure 1).

Figure 1. CCL18 levels released by mononuclear cells after stimulation with EVs and AT1R mab or isotype.

Stimulation with SSc EV + AT1R mab (n=4), HD EV + AT1R mab (n=3), AT1R mab control, SSc EV + isotype (n=4), HD EV + isotype (n=3) and isotype control. One-way ANOVA was used to test for statistical significance (p<0.05, **p<0.01, ***p<0.001).

Conclusion: The secretion of pro-fibrotic CCL18 by human monocytes in response to a monoclonal AT1R antibody as well as to SSc IgG indicates that anti-AT1R abs are involved in the SSc pathogenesis. Further, this effect could also be due to SSc-EVs potentially presenting anti-GPCR abs to their receptors on immune cells.

REFERENCES:

Disclosure statement: No conflicts with others exist.

Disclosure of Interests: None Declared.

DOI: 10.1136/annrheumdis-2023-eular.2964

AB0158 GENETIC EVIDENCE OF CASUAL ASSOCIATION BETWEEN POLYMYOSITIS AND RISK OF INTERSTITIAL LUNG DISEASE: A MENDELIAN RANDOMIZATION STUDY

Keywords: Lungs, Myositis

Z. J. Yuan1,2, R. Zhao1,2, M. K. Yao1,2, J. Y. Li1,2, S. Y. Liu1,2, Z. X. Zhang1,2,3, X. Li1,2,3, C. Wang1,2,3, Shaxi Medical University, Shaxi Provincial Key Laboratory of Rheumatism Immune Microeology, Taiyuan, China; 3Shaxi Medical University, Key Laboratory of Cellular Physiology, Taiyuan, China; 4The Second Hospital of Shaxi Medical University, Rheumatology, Taiyuan, China

Background: Polymyositis (PM) is an immunologically abnormal inflammatory myopathy, which is one of the common types of idiopathic inflammatory myopathies[1]. A global prevalence of approximately 41% of Interstitial lung disease (ILD) in PM patients has been estimated, which causes significant morbidity and mortality[2]. There have been a number of studies shown that PM and ILD may have similar pathogenesis, which focus on PM may induce ILD cellular immune system components[3]. While the two diseases may occur at the same time, but there is no directly evidence that the two diseases are causally related.

Objectives: Our study aimed to discover the casual association between PM and ILD, and determine the impact of PM on ILD.

Methods: We retrieved two large European genome-wide association study (GWAS) summary data of PM and ILD from MRC IEU OpenGWAS, which included 213,284 and 218,072 individuals, respectively. Single-nucleotide polymorphisms (SNPs) linked with disease were selected as instrumental variables (IVs) using genome-wide significance levels (P < 1 .0 × 10-5). And the Instrumental variables (IVs) were estimated. The two-sample Mendelian randomization (MR) method was applied to estimate the casual relationship of PM on ILD. The random-effects inverse variance weighted method (IVW) was mainly used to the MR analysis. Additionally, the horizontal pleiotropy effect was analyzed by MR-Egger and weighted median method sensitivity test. A leave-one-out analysis was conducted to avoid bias caused by a single SNP.

Results: Our study discovered that PM was considered as a risk factor of ILD. 15 SNPs strongly associated with PM were extracted from GWAS. The existence of PM may increase the risk of ILD by 1% (OR = 1.006, 95% CI: 1.001 - 1.016, p = 0.002) No single SNP significantly biased the causal effect of PM on ILD (Q = 0.18). No significant directional pleiotropy between PM and ILD was presented in the MR-Egger regression analysis.

Conclusion: This study provides evidence of an adverse effect of PM on ILD. And these may be meaningful for the prevention and intervention of PM and ILD. Meanwhile, our work also provides genetic statistical evidence for the study of the causal relationship of PM and ILD.

REFERENCES:

Downloaded from http://ard.bmj.com/ on July 22, 2023 by guest. Protected by copyright.
Systemic Scleroderma (SSc) is an autoimmune disease characterized by a wide range of clinical manifestations. One of the main targets of this pathology is the pulmonary system. In turn, SSc-associated damage of lung structures is characterized by a significant negative impact on the survival and quality of life of patients. Therefore, we aimed to assess the possible favorable influence of vitamin D3 and α-tocopherol acetate (ATA) on the morphological structure of the pulmonary system. In turn, SSc-associated damage of lung structures is characterized by a significant negative impact on the survival and quality of life of patients.

Background: Systemic scleroderma (SSc) is an autoimmune disease characterized by a wide range of clinical manifestations. One of the main targets of this pathology is the pulmonary system. In turn, SSc-associated damage of lung structures is characterized by a significant negative impact on the survival and quality of life of patients.

Objective: Therefore, we aimed to assess the possible favorable influence of vitamin D3 (VD3) and α-tocopherol acetate (ATA) on the morphological structure of lungs’ parenchyma in the experimentally induced SSc.

Methods: We assembled our experimental animals into three groups: a control group (CG) (20 animals), an experimental group (EG) #1 (25 animals), and #2 (25 animals). Experimental animals were mature laboratory rats, belonged to the Wistar line, and were 180-220 g of body weight. Animals in EG #1 were injected to intramuscular injections of ATA solution 10 mg of body weight, and of 200 μg of vitamin D3 according to the same scheme. In EG #2, rats were subjected to intramuscular injections of 10 μg of sodium hydrochloride (NaClO) according to the reported previously schedule [1] for SSc modeling purposes. Laboratory animals of the CG were receiving isotonic solution according to the same scheme. In EG #2, rats were subjected to intramuscular injections of ATA solution 10 mg/100 g of body weight, and of a VD3 solution 1000 IU/100 g of body weight for 3 weeks (second half of the experiment performance). All three groups of animals were removed from the experiment 8 weeks after its beginning. The lung tissue specimens were examined using light (Leica DM750, x200 magnification) microscopy. Data distribution were evaluated with descriptive statistics, and a p<0.05 was considered statistically significant. Statistical analysis was carried out using IBM SPSS version 26.

Results: The lung parenchyma samples obtained from CG did not show significant deviations from the normal histological picture. (Figure 1A). The histological analyses of lung specimens of experimental animals revealed non-specific interstitial pneumonia (NSIP) which is the most common type of SSc-associated interstitial lung disease (ILD) (Figure 1B). There were productive and sclerotic modifications of the interalveolar septum, their infiltration by the lymphoid and plasma cells with significant disfigurement of alveolar structure. (White arrow – alveolar wall thickening; black arrow – thickening of basal membrane of microvessels). After using VD3 and ATA animals demonstrated a distinct decrease in the intensity of lymphoid and plasma cells infiltration of interalveolar spaces (Figure 1C). Furthermore, the sclerotic alteration of the alveolar-capillary barrier was less prominent compared to EG #1 specimens. The Ashcroft score was significantly higher in EG#1 (3.7±0.6) compared to EG#2 (1.8±0.3) (p<0.05) and CG (0.6±0.1) (p<0.05).

Conclusion: This study confirms positive effect of vitamins D3 and α-tocopherol acetate on morphological structure of pulmonary parenchyma in the preclinical model of SSc.

REFERENCES: