of the descent, including 16,380,451 cases and 213,145 controls.[2] The data of PA, including accelerometer-based physical activity (APA), vigorous physical activity (VPA), moderate physical activity (MPA), and sedentary behavior (Time spent watching television (TV), Time spent using computer and Time spent driving) were available from UK Biobank dataset. To evaluate the causal association between PA and PM, the inverse variance weighted (IVW) method was conducted as the primary method. In sensitivity analyses, we used the MR-Egger method to evaluate the potential pleiotropy effects. Moreover, we also applied weighted median and MR-PRESSO to assess the presence of pleiotropy. Based on the result of IVW method, there was little evidence of causal associations of the remaining seven exposures with the risk of PM. (p > 0.05)(Figure 1).

Figure 1. Mendelian randomization analysis for gene-level causality between PA, sedentary behaviors, and PM were evaluated by the odds ratio (OR) values of IVW, MR Egger, and Weighted median. Forest plot (A), scatter plot (B), leave-one-out analysis (C) were used to assess the power of PA, MR, mendelian randomization; IVW, inverse-variance weighted method; MR-Egger, Mendelian randomization-Egger; SNP, single nucleotide polymorphisms; CI, confidence interval.

Conclusion: APA was causally associated with the risk of PM.

REFERENCES:


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AB0155

POTENTIAL DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF ANTI-CARBAMYLATED PROTEIN ANTIBODIES IN THE SPONDYLOARTHRITIS

Keywords: Spondyloarthritides, Biomarkers, Autoantibodies

E. Favole1, E. Grapsi1, M. Prete1, V. Racanelli1, F. Perosi1. 1University of Bari Medical School, Department of Interdisciplinary Medicine, Bari, Italy

Background: Spondyloarthritides (SpA) include a group of inflammatory rheumatic diseases with different clinical manifestations. The diagnosis of SpA is still a challenge in clinical practice, in that specific serological markers are still missing. Recently, anti-carbamylated protein antibodies (anti-CarP Ab) have been detected in patients with psoriatic arthritis (PsA) and their levels appear to be correlated with disease activity (p=0.047), plantar fasciitis (p=0.037) and family history of psoriasis (p=0.012). Anti-CarP Ab levels were also directly correlated with the presence of autoimmune thyroiditis in PsA subgroup (p=0.02), and with family history of psoriasis in E/A ASAS subgroup (p=0.016).

Conclusion: This study suggests an association of anti-CarP Ab levels and disease activity in peripheral E/A. Whether the presence of anti-CarP Ab in E/A ASAS may predict evolution in PsA remains to be assessed.

REFERENCES:

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AB0156

MECHANOTRANSDUCTION VIA MYOSIN II ISOMERS IN DEVELOPMENT OF SKIN FIBROSIS WITHIN SYSTEMIC SCLEROSIS

Keywords: Systemic sclerosis, Cytokines and chemokines, Skin

B. Russo1, M. Shutova1, G. Romanescu1, N. Bremilla1, W. H. Boehncke2.

1University of Geneva, Pathology and Immunology, Geneva, Switzerland; 2Hôpitaux Universitaires de Genève (HUG), Dermatology and Venereology, Genève, Switzerland

Background: Skin fibrosis, the hallmark of systemic sclerosis (SSc), is a complex inflammatory process leading to excessive extracellular matrix (ECM) deposition and increased stiffness in the dermis [1]. The mechanical properties of the extracellular environment can be sensed by the cells and transformed into intracellular signalling and gene expression regulation in the process of mechanotransduction. The upregulation of mechanotransduction has been linked to the progression of fibrosis in SSc, particularly through the Rho-ROCK-dependent myosin II pathway, which activates intracellular contractility [2]. Nonmuscle myosin II itself is expressed as three isoforms (NMHIIA, NMIIB, NMIIC) with common and unique functions. However, the specific role of Rho activation and distinct myosin isoforms in SSc pathogenesis is unknown.

Objectives: To investigate the role of NMIIC isoform regulation in the development of skin fibrosis in SSc.

Methods: The expression of NMIIA and NMIIB, as well as their activation through phosphorylation of Myosin Light Chain (MLC) were evaluated by immunofluorescence in primary fibroblasts from four SSc and four healthy donor (HD), which were stimulated with TGFβ. The NMIIC contractility was inhibited with Y-27632, a small molecule inhibitor of ROCK that phosphorylate MLC or blebbistatin, a small molecule that inhibit NMII. The production of IL-6 and type I collagen by fibroblasts was assessed by ELISA.

Results: We have observed a re-distribution of NMIIC isoforms within the intracellular contractile system and increased MLC phosphorylation in cultured SSc fibroblasts compared to HD. A similar phenotype was observed in HD fibroblasts primed with TGFβ. Treatment of TGFβ-primed HD fibroblasts with Y-27632 or blebbistatin substantially reduced IL-6 and collagen I production.

Conclusion: Our data point to an altered actomyosin cytokine dynamics and force distribution in SSc fibroblasts and indicate that NMIIC isoforms are required for the TGFβ-dependent secretion of inflammatory cytokines and collagen deposition by fibroblasts.

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AB0157

SYNERGISTIC EFFECT OF AT1R-AUTOANTIBODIES AND EXTRACELLULAR VESICLES IN SSC PATHOGENESIS

Keywords: Systemic sclerosis, Innate immunity, Autoantibodies

A. Hackel1, R. Akbarzadeh1, M. Leiber2, A. Müller2, G. Riemekasten1.

1University Clinic Schleswig-Holstein, Lübeck, Germany; Clinic of Rheumatology and Clinical Immunology, Lübeck, Germany
Background: Systemic sclerosis, a rare chronic inflammatory disease, are 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 [8]. 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 and EVs in the pathogenesis of SSC becomes evident [10].

Objectives: Here we decipher the immune response of peripheral blood monocytes mediated by anti-AT1R- 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 monocytic 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 mononuclear cells upon stimulation for 24h with the AT1R mab 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.

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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, S. X. Zhang1,2, X. L. Li1,2, C. Wang1,2,3, 1Shanxi Medical University, Shanxi Provincail Key Laboratory of Rheumatism Immune Microecology, Taiyuan, China; 2Shanxi Medical University, Key Laboratory of Cellular Physiolgoy, Taiyuan, China; 3The Second Hospital of Shanxi Medical University, Rheumatology, Taiyuan, China

Background: Polymyositis (PM) is an immunologically abnormal inflammatory myopathy, which is one of the common types of idiopathic inflammatory myopathy[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 interference of confounding factors, including smoking, drinking and BMI were eliminated. 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 = 1.008, 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 casual relationship of PM and ILD.

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