Rag2<sup>−/−</sup>Fra2<sup>tg</sup> mice showed no fibrosis or Lin<sup>gp38</sup> cell expansion. ECG parameters of Rag2<sup>−/−</sup>Fra2<sup>tg</sup> mice were not changed compared to control mice, indicating that inflammation is necessary to acquire Fra2-driven fibrotic phenotype and defects in the conduction system.

**Conclusion:** Fra2 overexpression and inflammation foster stromal cell-to-myofibroblast differentiation, leading to cardiac fibrosis and defects of the conduction system. Targeting this process might be a therapeutic strategy for SSc patients with disorders of cardiac involvement.

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**OP0187**

**RITUXIMAB AND CYCLOPHOSPHAMIDE COMPARISON FOR EFFICACY AND SAFETY IN THE PATIENTS WITH SYSTEMIC SCLEROSIS ASSOCIATED WITH INTERSTITIAL LUNG DISEASE**

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**Background:** Cyclophosphamide (CyP) is considered as a drug of choice for the treatment of interstitial lung disease (ILD) in the patients with systemic sclerosis (SSc). However, according to the literature, the use of CyP leads to rather limited and transient improvement of the pulmonary fibrosis. In this context the search for novel, more efficacious agents has been continued, such as attracting much attention rituximab (RTM).

**Objectives:** To compare the impact of CyP and RTM on SSc clinical manifestation and activity, and the safety of these agents in the open-label prospective non-randomized study.

**Methods:** 107 patients with the confirmed SSc diagnosis and ILD evidence based on HRCT findings were enrolled into the study. All patients received low-dose and moderate-dose prednisolone regimens. 36 patients (Group A) received parenteral CyP for 12±6 months at total dose 10±6,5 g (the average age 47±12 years, females 92%, SSc duration 5.0±4.8 years, diffused/localized forms 1.6/1), 71 patients (Group B) received RTM at total dose 1.4±0.6 g over the follow-up period 13.2±2 months (the average age 46±13 years, females 83%, SSc duration 5.6±4.4 years, diffused/localized forms 1.4/1); to 32 (45%) of them RTM was added to immunosuppressants due to inadequate efficacy of the latter. The time of follow-up was different for single and repeated application, respectively, and 14 days after the first injection for single and repeated application, respectively, and ear and lung tissues were collected for further evaluation.

**Results:** In Groups A and B the therapy was associated with significant decrease in mRss (p<0.009 and 0.001, respectively) and ESScG (p=0.00165 and 0.001, respectively). Increase in LVEF (61.8±7.3 % versus 63.6±7.3 %; p=0.02) was only observed in RTM-treated patients. Evaluation of EVC time course in Groups A and B revealed significant FVC increase (p=0.034 and 0.00045, respectively), with median increment about 5%. In Group A FVC 10% FVC increase was found in the third of the patients thus exceeding respective parameter in Group B (p=0.2). The patient percentage with FVC decrease by >10% was similar in both groups. During the follow-up period no change of the other studied parameters was observed.

The therapy was better tolerated in RTM-treated group: during RTM therapy adverse reactions emerged in significantly lower proportion of the patients (11/14%) compared with CyP-treated group (19/53%), p=0.0000.

**Conclusion:** Both agents effectively alleviated skin induration and ESScG, and significantly improved FVC. However, CyP use for a year slightly more frequently resulted in clinically significant FVC increase, probably due to low RTM cumulative dose. RTM was better tolerated compared to CyP. The study findings substantiate potential use of anti-B-cell therapy both as a first-line agent for ILD treatment in the patients with SSc, and in the event of CyP inefficacy of poor tolerability, especially in the patients with cardiopatopy.

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**OP0188**

**PATHOGENICITY OF FUNCTIONAL AUTOANTIBOIES AGAINST AT1R IN A MOUSE MODEL OF SYSTEMIC SCLEROSIS**

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**Background:** Systemic sclerosis (SSc) is an autoimmune connective tissue disease featured by autoimmunity, fibrosis and vasculopathy. Although many autoantibodies have been detected in the sera of patients with SSc, it is not clear whether they play a role in the pathogenesis of disease. It has been reported that autoantibodies against the angiotensin-II receptor type 1 (AT1R) are present in the sera of SSc patients and are associated with several clinical symptoms of the disease, suggesting that these autoantibodies may act as pathogenic drivers. Recently, our group has developed a novel mouse model for SSc by immunizing mice with human AT1R (hAT1R). From this model we were able to generate functional monoclonal antibodies agonizing AT1R.

**Objectives:** In the current study, we aim to clarify, whether B cells and antibodies directed against AT1R are involved in the pathogenesis of experimental SSc in vivo.

**Methods:** To investigate the role of B cells in the hAT1R-induced mouse model of SSc, we immunized B-cell deficient mice with hAT1R. Nine weeks after the first immunization, mice were sacrificed and sera and tissues were collected for further evaluation. To investigate the pathogenicity of anti-AT1R antibodies in the disease, monoclonal autoantibodies against hAT1R were applied to the ear of C57Bl/6 mice by single or repetitive injection. Mice were sacrificed 24 hours or 14 days after the first injection for single and repeated application, respectively, and ear and lung tissues were collected for further evaluation.

**Results:** Compared to the wild type C57Bl/6 mice, hAT1R-immunized B-cell deficient mice were resistant against experimental SSc with regard to autoantibody production, inflammation in the lung and skin, and skin fibrosis. Furthermore, both single and repetitive injection of monoclonal antibodies against hAT1R induced inflammation in ears of mice. Despite this local effect, repetitive injection of anti-AT1R monoclonal antibodies provoked also inflammation in the lung of mice.

**Conclusion:** Our data demonstrate that i) B cells are indispensable for the pathogenesis of the hAT1R-induced mouse model for SSc and ii) monoclonal antibodies against hAT1R can induce inflammation in mice. Therefore, our results support a role of autoantibodies against AT1R in the pathogenesis of SSc.

**REFERENCES:**

Disclosure of Interests: Junping Yin: None declared, Xiaqing Wang: None declared, Xianqiu Chen: None declared, Gabriela Riemekasten: Consultant for: Chugai, F. Hoffmann-La Roche, Speakers bureau: Chugai, F. Hoffmann-La Roche, Xinhua Yu: None declared, Frank Petersen: None declared


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Genetics, epigenetics and immunity

OP0189 GENETICS OF JUVENILE IDIOPATHIC ARTHRITIS: THE IDENTIFICATION OF A NOVEL RISK LOCUS AND CLINICAL SUBGROUP ANALYSIS

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Background: Juvenile idiopathic arthritis (JIA) is a clinically heterogeneous group of childhood onset inflammatory joint diseases with strong evidence to support a genetic contribution to susceptibility. JIA is divided into seven clinical subgroups based on observed patterns of clinical symptoms using the International League of Associations for Rheumatology (ILAR) classification system. The genetic overlap between these groups is not completely understood and this lack of knowledge typically leads to the different ILAR groups being analysed as discrete entities and reducing the overall power of genetic association studies.

Objectives: The aim of this study was to conduct a large case-control association study on susceptibility to JIA to identify novel susceptibility loci and to investigate differences of these associations between the ILAR groups.

Methods: JIA participants were genotyped on the Illumina Infinium CoreExome or OmniExpress arrays at The University of Manchester. UK population control genotype data was obtained from the Understanding Society Longitudinal Study. Quality control of data was performed conforming to conventional standards based on call rate, cryptic relatedness and ancestry outliers. Imputation was performed using the Haplotype Reference Consortium panel on the Michigan Imputation Server followed by exclusion of SNPs with low imputation accuracy (R<0.5) and low minor allele frequency (<1%). Association testing of all SNPs was performed with an additive model incorporating imputation uncertainty using SNPTTEST. A subset of SNPs independently associated with all JIA (p-value<5x10^-8) were tested to evaluate if they were specific to a particular ILAR group or shared across multiple ILAR groups using Bayesian multinomial regression and model selection methods implemented in the Trinculo software package.

Results: Following quality control the dataset consisted of >7.4 million SNPs for 3305 JIA cases and 9196 controls. Association testing in a combined dataset of all ILAR groups identified seven SNPs associated at genome-wide significance (5x10^-8); six of these have previously been reported for JIA while one is a novel association. The novel association (rs497523, p-value = 7.12x10^-9, OR 0.85, 95% CI 0.80-0.9) maps to chromosome 16p11 and is located within intron one of the CCDC101 gene. In a subset of 44 independently associated SNPs we found no strong evidence to support association of any SNP to a specific ILAR group with the majority of the SNPs showing evidence for sharing across multiple groups.

Conclusion: In the largest case-control association study for susceptibility to JIA performed to date, we identified a novel association to a SNP in the intron of CCDC101. This gene is involved in transcriptional regulation through histone acetyltransferase. CCDC101 may be the causal gene at this locus; however introns contain enhancer elements that regulate other genes in the transcriptional domain. Therefore fine mapping with the integration of genomic data is currently being performed for this locus. The results provide little evidence to support ILAR subgroup specificity for any of the associated variants; on the contrary the results support a general model of sharing across multiple groups. The combined analysis of data across subgroups, informed by model sharing, will maximise power to identify novel associations.

Disclosure of Interests: None declared


OP0190 META-ANALYSIS OF IMMUNOCHEMICAL DATA OF FOUR AUTOIMMUNE DISEASES REVEALS NOVEL SINGLE-DISEASE AND CROSS-PHENOTYPE ASSOCIATIONS

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Background: In recent years, research has consistently proven the occurrence of genetic overlap across autoimmune diseases, which supports the existence of common pathogenic mechanisms in autoimmunity.

Objectives: The objective of this study was to further investigate this shared genetic component.

Methods: We performed a cross-disease meta-analysis of immunochip data from 37,159 participants diagnosed with a seropositive autoimmune disease (11,485 celiac disease (CeD), 15,523 rheumatoid arthritis (RA), 3,477 systemic sclerosis (SSc), and 6,670 type 1 diabetes (T1D)) and 22,308 healthy controls of European origin using the R package ASSET.

Results: We identified 38 risk variants shared by at least two of the conditions analyzed, five of which represent new pleiotropic loci in autoimmunity. We also identified six novel genome-wide associations for the diseases studied. Cell-specific functional annotations and biological pathway enrichment analyses suggested that pleiotropic variants may deregulate gene expression in different subsets of T cells, especially Th17 and regulatory T cells. Finally, drug repositioning analysis evidenced several drugs that could represent promising candidates for CeD, RA, SSc and T1D treatment.

Conclusion: We have been able to advance in the knowledge of the genetic overlap existing in autoimmunity, thus shedding light on common molecular mechanisms of disease and suggesting novel drug targets that could be explored for the treatment of the autoimmune diseases studied.

REFERENCES:

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