Objectives: The purpose of the effort was to increase patient safety and to ensure that patients received independent patient information within biological drugs.
Methods: First the Association conducted a small study of how the shift of drug had taken place in the different regions. Most patients experienced that they were told by the doctors to shift to biosimilars, and furthermore they experienced a lack of information about the new biosimilars. On a national level, nearly all patients on a biological drug are registered in a national database. It is registered in the database and hospital records which drug the patient are prescribed, but it is not registered on a batch-level.
In order to change these conditions the Association started a dialog with the politicians and the authorities on a national level and the hospital-administrations on a regional level. The purpose was to improve the registration of the drugs on batch-level, to improve more independent patient information and to improve the involvement of the patient in the decision making process. The dialog was on a general level, but with several patient-stories from each region.
Results: A new national plan for better monitoring and information about biologic and biosimilars was launched in august 2015 and carried out in 2016. The plan consists of four parts: 1) Monitoring biological drugs and biosimilars on batch level, 2) Information campaign to health professionals and patients, 3) Digital solutions and easy reporting of side effects from health professionals and patients, 4) Focus on monitoring patient safety by the authorities. The Danish Rheumatism Association has participated in the work to implement the plan. In addition to the national plan the hospitals on a regional level, has invited the Rheumatism Association to participate with a representative in the working group, where national recommendations for the use of biological drugs are being made in an attempt to involve the patient perspective more. The content of the national plan and the involvement in the work with national recommendations, will be elaborated and discussed from the patients perspective throughout the presentation.
Conclusions: The implementation of biosimilars created great insecurity among patients. Therefore, the Danish Rheumatism Ass. decided to make an effort to create better patient information and safety for the patients. Through dialog with politicians, national authorities and hospital-administrations, we managed to get a national plan for better monitoring and information about biologic and biosimilars, and to be involved in the work with national recommendations for these drugs. The national plan and work with national recommendations will be elaborated in the presentation.
Disclosure of Interest: None declared
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FRIDAY, 16 JUNE 2017

Switching T on and off: how T cells drive and regulate chronic inflammation

OP0329 INVOLVEMENT OF T HELPER 17 CELLS IN INFLAMMATORY ARTHRITIS DEPENDS ON THE HOST INTESTINAL MICROBIOTA

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Background: Intestinal microbiota have been associated with psoriatic and rheumatoid arthritis. One of the major effects of microbiota is the induction of mucosal T helper 17 (Th17) cells. We therefore reasoned that the efficiacy of Th17-targeted therapies in arthritis may depend on the host microbiota. Previous studies focused on the role of the cytokine interleukin-17A (IL-17), rather than Th17 cells, by using IL-17 inhibitors or IL-17-deficient mice. Therefore, the role of Th17 cells, which produce multiple pro-inflammatory mediators in addition to IL-17, is not yet fully understood.
Objectives: The aim of this study was to determine the role of Th17 cells, beyond the cytokine IL-17, in arthritis, and to investigate whether Th17 cells are differentially involved in arthritis depending on the microbiota present.
Methods: We established conditional Th17-deficient mice, which exhibit a CD4-Cre-induced floxing of a part of the Rorc allele that encodes the Th17 master regulator RORγt. We compared the development of collagen-induced arthritis in Th17-deficient (CD4-Cre$^+$ Rorc$^{flox/flox}$) and -sufficient (CD4-Cre$^-$ Rorc$^{flox/flox}$) littermate mice, either colonized with known Th17 cell inducers segmented filamentous bacteria (SFB) or harboring the SFB-free Jackson microbiota. The abundance of Th1 and Th17 cells and the production of IL-17, IFNγ and GM-CSF were quantified by flow cytometry and multiplex cytokine assay.
Results: CD4-Cre$^+$ Rorc$^{flox/flox}$ mice had significantly lower Th17, but similar Th1 cell abundance, in intestinal lamina propria compared with Cre$^-$ littermate controls. Surprisingly, the total amount of IL-17A production by all lamina propria cells during arthritis was rather increased in Th17-deficient mice, with CD8$^+$ T cells and Gr1$^+$ neutrophils being the main alternative sources of IL-17. Despite this increased total IL-17 levels, conditional Th17-deficient mice developed a less severe arthritis compared with Th17-sufficient mice when intestinal microbiota comprised SFB. This suggests a role for Th17 cells in inflammatory arthritis distinct from IL-17. Accordingly, synovial inflammation, cartilage destruction and proteoglycan depletion were reduced in SFB-colonized Th17-deficient mice. While the production of IL-17 by joint-draining lymph node cells stimulated with PMA and ionomycin was similar between Th17-sufficient and –deficient mice, cells from the latter group produced significantly less IL-17 upon antigen-specific stimulation with type II collagen. Furthermore, the production of GM-CSF, another Th17 cell-derived cytokine, was significantly lower in the lymph nodes of Th17-deficient mice, an effect associated with the protection against arthritis. Importantly, substitution of the intestinal microbiota with SFB-free Jackson microbiota resulted in the loss of Th17 cell dependency of arthritis as Th17-sufficient and –deficient mice showed similar disease progression under this condition.
Conclusions: These data suggest that Th17 cells may mediate inflammatory arthritis partly through IL-17-independent mechanisms. Our observations also suggest that the involvement of Th17 cells in arthritis depends on the microbiota subset present in the host. Therefore, a microbiome-guided stratification of rheumatoid or psoriatic arthritis patients might improve the efficacy of Th17 (or IL-17)-targeted therapies.
Disclosure of Interest: None declared
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OP0330 FRA2 OVEREXPRESSION LEADS TO SYSTEMIC AUTOIMMUNITY BY DECREASING IL-2 RESPONSIVENESS AND THYMIC TREG DEVELOPMENT

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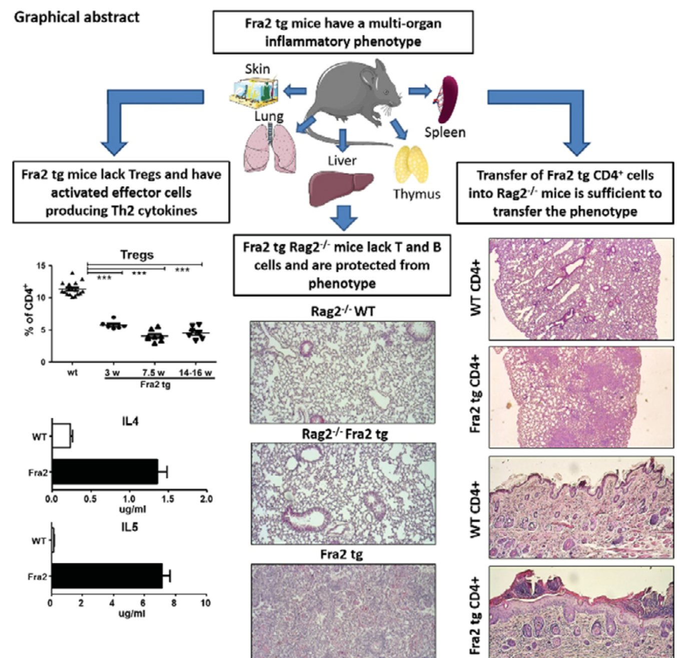
Background: Fos-related antigen 2 (Fra2) is a transcription factor belonging to the Fos family proteins which is part of the AP-1 transcription complex. We recently described a Fra2 transgenic (tg) mouse model which develops a multi-organ inflammatory phenotype affecting skin, lungs, thymus, liver and salivary glands. We have observed abnormalities in the T cell compartment, particularly in regulatory T (Treg) cells, which led us to hypothesize that Fra2 tg mice develop a T cell driven autoimmune phenotype.
Objectives: To demonstrate the autoimmune phenotype of Fra2 tg mice and to characterize the mechanisms leading to Treg cell abnormality.
Methods: We used previously generated Fra2 tg overexpressing mice. T lymphocyte populations were analyzed by flow cytometry for expression of activation markers and secretion of cytokines. We transferred purified CD4+ T cells into Rag2-/- mice lacking T and B cells, and we generated Rag2-/-Fra2 tg mice. Bone marrow cells were transferred into lethally irradiated recipients to create Fra2-WT bone marrow chimeric mice.
Results: Fra2 tg mice backcrossed onto a Rag2$^{-/-}$ background did not develop inflammatory manifestations (n=6), demonstrating the dependence on T and/or B cells of the autoimmune phenotype. In line with this, the transfer of purified CD4$^+$ cells from 16 week-old Fra2 tg mice into Rag2$^{-/-}$ recipients was sufficient to transfer the disease phenotype (n=3). Analysis of T cell populations from Fra2 tg mice showed the presence of activated CD4$^+$ and CD8$^+$ cells in the spleen



and lungs. After *in vitro* stimulation, we found that $CD4^+$ T cells from Fra2 tg mice produced the Th2 cytokines IL-4, IL-5 and IL-13. Thus, these data strongly suggest a T cell-driven autoimmune disease in these mice.
We previously reported a striking decrease of Treg cells in Fra2 tg mice, which might explain the autoimmune phenotype observed. Supporting this idea, we found that 3 week-old mice were devoid of organ manifestations and of T cell activation, but presented the same defect in the Treg cell population (n=6, $p<0.001$). Analysis of thymuses from these young tg mice showed an abnormal development of thymic Treg (tTreg) cells. In particular, we could observe a normal population of tTreg precursors ($CD4^+CD8^-CD25^+FoxP3^-$), but a strong decrease in mature tTreg cells ($CD4^+CD8^-CD25^+FoxP3^+$, n=4), suggesting a perturbation in the transition from tTreg precursors to mature tTreg cells in Fra2 tg mice. We also found that *in vivo* stimulation with IL-2 failed to induce the proliferation of Treg cells in Fra2 tg mice compared to WT mice, suggesting that Fra2 overexpression affects IL-2 sensitivity of T cells. Finally, Fra2-WT bone marrow chimera mice also displayed a decreased percentage of Tregs confirming a cell-intrinsic and hematopoietic role of Fra2 in Treg cell development.
Conclusions: Our data suggest that Fra2 controls tTreg cell development, possibly by modulating IL-2 signaling in T cells, which leads to autoimmunity in this mouse model. This new pathway could be targeted in a translational approach to modulate the capacity of T cells to differentiate in Tregs during autoimmune disease.
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SATURDAY, 17 JUNE 2017

Reverse translation - learning from clinical trials in SLE, Sjögren's and APS

OP0331 A NOVEL HUMANIZED EFFECTOR-DEFICIENT FCYRIIA ANTIBODY INHIBITS IMMUNE COMPLEX MEDIATED PROINFLAMMATORY RESPONSES

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Background: Collectively, the cell surface Fc region of IgG receptors (FcγRs) engage soluble IgG and IgG containing immune complexes and trigger activation or inhibtory signals that play a critical role in the regulation of immune responses. The low affinity FcγRIIA (CD32A) is the most widely expressed activating FcγR in humans and appears to drive autoantibody and immune complex mediated autoimmune disorders. So far a therapeutic targeting this receptor has not been developed.
Objectives: To generate and characterize a novel humanized effector-deficient FcγRIIA antibody (MEDI9600) for clinical development.
Methods: The mode of action of MEDI9600 was assessed by confocal microscopy, whole blood internalization, and binding competition assays. Multiple cell based assays were used to measure autoantibody and immune complex mediated responses.
The safety of MEDI9600 was assessed in *in vitro* by neutrophil migration, activation and opsonophagocytic killing assays. Safety and pharmacokinetics were examined *in vivo* in a single-dose PK/PD study in cynomolgus monkey.
Results: We generated a humanized effector-deficient FcγRIIA antibody (MEDI9600) that potently blocks both autoantibody and immuno complex-mediated proinflammatory responses from a variety of cell types. This includes the inhibition of Toll-like receptor stimulatory immune complexes that induce type I Interferons from pDC, and the inhibition of anti-neutrophil cytoplasmic antibody (ANCA) induced production of reactive oxygen species from neutrophils, which are associated with the pathogenesis of systemic lupus and ANCA vasculitis respectively. MEDI9600 specifically binds FcγRIIA and its suppressive activity is attributed to its capacity to block ligand engagement and to internalize the receptor from the cell surface. Moreover, *in vivo* studies indicate that MEDI9600 has a favorable pharmacokinetic and safety profile.
Conclusions: We have generated MEDI9600, a specific humanized antibody antagonist of FcγRIIA with null effector function that may provide a novel therapeutic approach in the treatment of immune complex mediated diseases.
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SATURDAY, 17 JUNE 2017

Genomic imprinting and post-translational modifications

OP0332 THE GENOMIC ARCHITECTURE OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) BY RNA-SEQ: DISTINCT DISEASE SUSCEPTIBILITY, ACTIVITY AND SEVERITY SIGNATURES AND EXTENSIVE GENETIC EFFECTS ON WHOLE BLOOD GENE EXPRESSION

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Background: SLE displays significant immunological and clinical heterogeneity. Understanding the molecular basis of this variability may facilitate early diagnosis, risk stratification and personalized therapy.
Objectives: To perform full transcriptome analysis in SLE patients in order to identify molecular sub-phenotypes and explore the genomic basis for the disease susceptibility and severity.
Methods: Whole blood mRNA and genomic DNA were extracted from 142 SLE patients with varying levels of disease activity/severity and 48 matched healthy volunteers. Paired-end RNA sequencing was performed using the Illumina HiSeq 2000 platform and genotyping with the Infinium CoreExome followed by imputation from the 1000 Genomes. To integrate blood transcriptome with genotype data we used the enrichment analysis of expression-quantitative trail loci (eQTLs). The CIBERSORT tool was used to provide an estimation of the abundancies of different circulating immune cell types.
Results: We found a large number (6730, 5% False Detection Rate [FDR]) of differentially expressed genes (DEGs) between SLE patients and controls. Interferon signaling was significantly upregulated in SLE with most of the DEGs (146 out of 281) being regulated by both type I and type II interferon. Analysis of the blood composition in different immune cell types revealed global upregulation of type I interferon and antiviral response genes as well as immune cell-specific alterations in gene expression in SLE patients. Comparison of the transcriptome in active/inactive SLE and healthy individuals identified distinct "disease susceptibility" and "disease activity" gene signatures encompassing 2738 and 377 DEGs, respectively. Analysis according to individual organ involvement revealed more widespread aberrancies in gene expression in SLE patients with active nephritis as compared to activity from other organs, corresponding to oxidative phosphorylation, granulocyte activation and antimicrobial humoral response pathways. By integration of genotyping data, we mapped a total 3142 (5% FDR) *cis*-eQTLs in SLE patients suggesting extensive genetic effects on whole blood gene expression. Importantly, linear discriminant analysis enabled the definition of a set of DEGs which discriminated SLE versus healthy state with median sensitivity 83% and specificity 100%. Design of gene expression panels and expression profile/clinical trait correlation matrices for improved diagnostics, stratification and personalized therapy is in progress.
Conclusions: Specific gene networks confer susceptibility to SLE as well as to severe forms of the disease. These results may facilitate the early diagnosis, monitoring and prognosis, and the molecular taxonomy of SLE patients into pathophysiologically and prognostically distinct subsets for personalized therapy.
Disclosure of Interest: None declared
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