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

B. Chen[1], K. Vousden[2], S. Turman[1], H. Sun[1], S. Wang[1], L. Vinall[2], B. Kemp[2], S. Kasturiangan[1], E. Grant[1], M.J. Hinrichs[1], S. Eck[1], A. DiGiandomenico[1], X. Xiong[1], J. Griffiths[1], R. Herbst[1], D. Close[2], R. Kolbeck[1], G. Sims[1].
[1]MedImmune Inc, Gaithersburg, United States; [2]MedImmune Inc, Granta Park, United Kingdom

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.
Disclosure of Interest: None declared
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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

G. Bertsias[1,1,2,2], N. Panousis[3], I. Gergianaki[1,2], M. Tektonidou[4], M. Trachana[5], C. Pamfil[6], A. Fanouriakis[7], E. Dermitzakis[3], D. Boumpas[2,7,8,9,10].
[1]Rheumatology, Clinical Immunology and Allergy, University of Crete School of Medicine; [2]Laboratory of Autoimmunity and Inflammation, Institute of Molecular Biology-Biotechnology, FORTH, Iraklio, Greece; [3]Institute for Genetics and Genomics in Geneva, University of Geneva Medical School, Geneva, Switzerland; [4]Medical School, National and Kapodistrian University of Athens, Athens; [5]1st Department of Pediatrics, Aristotle University, Thessaloniki, Greece; [6]Iuliu Haţieganu University of Medicine and Pharmacy, Cluj, Romania; [7]4th Department of Medicine; [8]Joint Rheumatology Program, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece; [9]Medical School, University of Cyprus, Nicosia, Cyprus; [10]Laboratory of Autoimmunity and Inflammation, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

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.
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