DENDRITIC CELL-DERIVED IL-27 REGULATES THE MAGNITUDE OF INDUCIBLE ECTOCYTIC GERMINAL CENTRES BUT FAILS TO MODULATE IL-17 PRODUCTION IN CD4 T CELLS FROM PATIENTS WITH SJÖGREN’S SYNDROME

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Background: Approximately 30% of Sjögren’s Syndrome (SS) patients develop ectopic lymphoid structures (ELS) in their salivary glands (SG). ELS play an active role in autoimmunity and contribute to the development of MALT lymphomas. Interleukin 27- (IL-27) exerts key immunomodulatory actions on CD4 T cells with both pro and anti-inflammatory roles but its role in the formation and regulation of ELS in the salivary glands of SS is unknown.

Objectives: We first used a murine model of inducible SG EL27 to elucidate the role of IL-27 and its interaction with IL-17 in the regulation of ELS formation and function. We then extended our observations on a cohort of SS patients to identify IL-27 cellular source, target cells and functional properties in modulating peripheral and lesional CD4 T cells function.

Methods: To trigger ELS formation a single dose of reporter-encoding adenovirus was delivered intranasally to the SG of IL-27–/– deficient (KO) mice. For IL-17 blockade anti-mouse IL-17A antibody was administered systemically. ELS development and peripheral immune responses were tracked by immunohistopathology, FACS, and qPCR. Minor SG biopsies were collected from SS and non-specific sialadenitis (sicca) patients. Peripheral blood mononuclear cells isolated from SS and non-specific sialadenitis (sicca) patients were cocultured with autologous DCs and parotid gland MDCs were incubated with IL-27 and analysed by FACS for CD4 T cell subset cytokine release upon IL-27 incubation. We did not observe any difference in IL-27R expression by ELISA as indicative of the IL-12 and IL-23 pathways, respectively, and an IFN-γ response in the SG of SS patients suggesting that a profound dysregulation of the IL-27/Foxp3 axis play an important role in ELS formation in this condition.

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RNA SEQUENCING AND MACHINE LEARNING TECHNIQUES PREDICT MAJOR ORGAN INVOLVEMENT IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Both clinically and molecularly, Systemic Lupus Erythematosus (SLE) is a heterogeneous disease with non-synchronous multi-organ involvement of varying severity, and alternating periods of remission and flares. There is an unmet need for a blood-based “liquid biopsy” to predict prognosis of the disease.

Objectives: To determine the smallest set of genes predicting SLE organ involvement and disease activity using RNA-sequencing data derived from whole blood cells from 150 SLE patients and machine learning techniques.

Methods: Disease activity was measured by the SLE disease activity index-2000 (SLEDAI-2k) and by organ involvement (treated as binary outcomes). SLEDAI-2k: mild-moderate disease (SLEDAI 0-8), severe (SLEDAI >8). Organ involvement: major (renal, heart, lung, nervous system, and SLEDAI-2K kidney) and minor (all others). The RNA-sequencing dataset was pre-processed to assemble 20,368 genes and then split in training/validation data. Two feature selection steps (edgeR and recursive feature elimination) were used to remove noise and keep the smallest set of genes which best predicts each outcome. Different prediction models were fit to identify which one performs best using the gene signature selected in the previous step.

Results: Two gene signatures were kept after feature selection to predict each of the two outcomes (25 genes for organ involvement; 50 genes for SLEDAI-2k). Organ involvement was predicted with high accuracy (accuracy=0.89, specificity=0.88 in the validation data) using the elastic net generalised linear model. Among the 25 best predictors were MPO, ITGA3 and CD38. SLEDAI-2K could not be predicted with high accuracy by any model.

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BIOMARKER PROFLING REVEALS NOVEL MECHANISTIC INSIGHTS INTO USTEKINUMAB THERAPEUTIC RESPONSES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease that causes progressive organ damage. The cytokines type I interferon (IFN-I), IL-12 and IL-23 have all been shown to contribute to SLE pathogenesis. We previously reported that treatment with ustekinumab (UST), an anti-IL-12/IL-23 p40 neutralizing monoclonal antibody, improved global and organ-specific measures of disease activity in a randomized, placebo (PBO)-controlled study of patients with active SLE (NCT02349061). Here, we utilized biomarker data from this clinical study to elucidate the mechanism of action of UST in SLE.

Objectives: We aimed to determine whether modulation of IL-12, IL-23, or both cytokines in SLE was necessary for the clinical benefit of UST in SLE. To address this question, we performed a gene expression analysis of UST and PBO treated patients, and identified genes which were differentially regulated and had the potential to mediate the clinical benefit of UST in SLE.

Methods: A Phase 2, placebo-controlled study enrolled 102 patients with active SLE (NCT02349061). Here, we utilized biomarker data from this clinical study to elucidate the mechanism of action of UST in SLE. We aimed to determine whether modulation of IL-12, IL-23, or both cytokines in SLE was necessary for the clinical benefit of UST in SLE. To address this question, we performed a gene expression analysis of UST and PBO treated patients, and identified genes which were differentially regulated and had the potential to mediate the clinical benefit of UST in SLE.

Results: To detect the smallest set of genes predicting SLE organ involvement and disease activity using RNA-sequencing data derived from whole blood cells from 150 SLE patients and machine learning techniques.

Methods: Disease activity was measured by the SLE disease activity index-2000 (SLEDAI-2k) and by organ involvement (treated as binary outcomes). SLEDAI-2k: mild-moderate disease (SLEDAI 0-8), severe (SLEDAI >8). Organ involvement: major (renal, heart, lung, nervous system, and SLEDAI-2k kidney) and minor (all others). The RNA-sequencing dataset was pre-processed to assemble 20,368 genes and then split in training/validation data. Two feature selection steps (edgeR and recursive feature elimination) were used to remove noise and keep the smallest set of genes which best predicts each outcome. Different prediction models were fit to identify which one performs best using the gene signature selected in the previous step.

Results: Two gene signatures were kept after feature selection to predict each of the two outcomes (25 genes for organ involvement; 50 genes for SLEDAI-2k). Organ involvement was predicted with high accuracy (accuracy=0.89, specificity=0.88 in the validation data) using the elastic net generalised linear model. Among the 25 best predictors were MPO, ITGA3 and CD38. SLEDAI-2k could not be predicted with high accuracy by any model.

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