Results Consistent with previous reports, SARD patients had increased proportions of activated B cells ($CD86^+$ or $CD95^+$) and in the SLE patient subset there were increased proportions of plasma cells/plasmablasts, as compared to ANA^- controls. SARD patients also had reduced proportions of iNKT and IFN-γ producing cells, as well as, increased proportions of memory Tfh ($CD4^+CXCR5^{hi}PD1^{hi}$) and T regulatory (Treg, $CD4^+FOXP3^+HELIOS^+$) cells, especially in the SLE and Sjogren's Disease patient subsets. In asymptomatic ANA^+ individuals and UCTD patients, similar increases in the proportion of activated B cells, Tfh, and Treg cells, and decreases in the proportion of iNKT and IFN-γ producing cells were seen to those in SARD. In asymptomatic ANA^+ individuals and SARD patients, the extent of serologic changes (number of specific ANAs detected by Bioplex® 2200 ANA screening system) positively correlated with activation in the switched memory B cell compartment and the proportion of Tfh cells, with the later being an independent predictor of serologic status in a multivariate analysis. However, significantly elevated levels of Tfh cells could still be seen in asymptomatic ANA^+ individuals who lacked specific ANAs. Consistent with a role for Tfh cell in ANA production there was a strong correlation between the proportion of Tfh and plasma cells in asymptomatic ANA^+ individuals. In preliminary studies, the majority of Tfh cells in asymptomatic ANA^+ and UCTD patients were Tfh2 cells, with a trend to increased proportions of Tfh2 cells and decreased proportions Tfh17 cells as compared to active SLE patients.

Conclusions Tfh cells appear to play an important role in the development of a positive ANA and in the epitope spreading that may accompany disease progression, and therefore constitute a promising target for treatment of early disease.

AI-10 TFH CELLS AND B-CELL SELECTION

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Background and methods Initiation of a thymus-dependent humoral immune response requires interaction of activated B cells and follicular B helper T (Tfh) cells, a specialized subset of CD4 T helper (Th) cells. Differentiation of Tfh cells leads to their localization to B cell follicles and germinal centers (GC) of secondary lymphoid organs, with their expression of costimulatory proteins and secretion of cytokines promoting GC B-cell proliferation, immunoglobulin gene hypermutation, and development of B-cell memory and long-lived plasma cells.

Results and conclusions The transcriptional repressor Bcl6 acts cell autonomously to drive a Tfh-cell development program, including upregulation of proteins necessary for function, with environmental signals promoting differentiation of these cells at the expense of other CD4 T-cell subsets. Tfh cells undergo differentiation within the GC, in part mediated by STAT4 and STAT6-driven chromatin remodeling, enabling differential cytokine production and consequent help to B cells, with affinity selection of the latter promoted by regulatory GC T cells. Therapeutically, blockade of Tfh-GC B interactions interrupts end-organ disease in the systemic autoimmune disease lupus, while resetting the Tfh-cell phenotype toward normal homeostasis.

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AI-11 THE KINASE INHIBITORY REGION OF SUPPRESSOR OF CYTOKINE SIGNALING-1 MODULATES AUTOINFLAMMATORY SKIN PATHOLOGY

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Background Although aberrant antibody production is a lupus disease hallmark, abundant evidence implicates a dysregulated peripheral T lymphocyte repertoire in the onset and progression of lupus. Notably, the intracellular protein suppressor of cytokine signaling-1 (SOCS1) has been shown to regulate T lymphocyte effector functions and modulate lupus-like pathologies in rodent models. Significantly, peritoneal injection of a peptide (SOCS1-KIR), capable of mimicking SOCS1, was effective in mitigating T lymphocyte effector functions associated with lupus disease progression. Moreover, topical application of SOCS1-KIR 'eyedrops' was effective in mitigating experimental autoimmune uveitis. The peptide has been shown to function through the inhibition of the janus kinases Jak2 and Tyk2. We have previously shown that peritoneal injection of SOCS1-KIR inhibited lymphadenopathy in MRL lpr/lpr mouse model of spontaneous lupus that was correlated to decreased frequencies of interferon gamma producing memory T cells (Collins et al, 2018 (under revision)). In addition, the peritoneal injection of SOCS1-KIR also inhibited spontaneous lesion formation=In this study we test the hypotheses that SOCS1 modulates skin pathology and that topical application of the SOCS1-KIR peptide will have efficacy in the imiquimod induced lesion model.

Methods SOCS1 heterozygous mating pairs, sufficient and deficient of interferon gamma, were obtained from St. Jude and used to generate mice used in the experiment. Spontaneous skin lesions were assessed by histology. In addition, cytokine neutralizing antibodies were administered to evaluate mechanisms promoting lesion formation. Imiquimod was administered in the presence or absence of SOCS1-KIR to mice sufficient and deficient in SOCS1. Lesion formation was subsequently assessed.

Results SOCS1 ± IFN gamma -/- mice, but not SOCS ±, or IFN gamma -/- spontaneously developed epidermal hyperplasia. The SOCS1 ±, IFN gamma skin lesions were heavily infiltrated with macrophages and IL17 producing T lymphocytes. In addition, imiquimod induced skin lesions were exacerbated on SOCS1 ± mice compared to WT. Significantly, the topical administration of SOCS1-KIR to imiquimod treated murine skin reduced epidermal hyperplasia, erythema, and scaling.

Conclusions Together these results suggest that a peptide mimic of SOCS1 may have value as a therapeutic for lupus through topical and/or systemic administration.

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