Conclusion Our study reveals that ABCs, a unique B cell subset, rely on Zeb2 expression and regulation. Zeb2 affects germinal center B cell development and dictates ABC identity. Modulating Zeb2-mediated Jak-Stat signaling could effectively curb ABC accumulation and related autoimmunity, presenting a potential therapy for autoimmune diseases.

205 LOCAL TISSUE MICROENVIRONMENT REGULATES T CELL PHENOTYPES IN MURINE SYSTEMIC LUPUS ERYTHEMATOSUS

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Background T cells play a significant role in the pathogenesis and end-organ damage observed in systemic lupus erythematosus (SLE). Previous studies using murine SLE models have demonstrated that kidney infiltrating T cells (KITs) differ substantially from their peripheral counterparts. Notably, KITs exhibit greater heterogeneity, characterized by a prominent population of resident memory and exhausted/dysfunctional T cells, along with a transitional or early exhausted population. In this study, our aim was to investigate T cell heterogeneity in multiple organs affected by SLE. We hypothesized that T cells isolated from different target organs would display distinct functional and transcriptional programs influenced by tissue-specific reprogramming. Additionally, we expected isolated clonal expansion in each target organ, with less clonal expansion in the spleen.
Methods Using the MRL. Fas^{lpr} model, which recapitulates numerous features human SLE, we isolated CD4 and CD8 T cells from five organs commonly impacted in SLE: kidney, liver, lung, spleen, and skin. T cells were obtained from female mice (18 wks or older) and male mice (26 wks or older). Single cell suspensions were prepared through chemical and mechanical dissociation. High-dimensional flow cytometry, metabolic analysis, functional studies, and scRNA-seq and TCR-seq were performed to analyze T cell heterogeneity.
Results Our findings revealed substantial variability in T cell function, metabolism, and phenotype across the different organs examined. Consistent with previous observations, the spleen was comprised of mainly effector T cells. Similar findings were observed in mucosal tissue associated infiltrating T cells isolated from lung and skin, which exhibited increased cytokine production, glucose uptake, and enhanced mitochondrial membrane potential. Conversely, T cells infiltrating solid organs such as the kidney and liver exhibited a more suppressed/exhausted phenotype, characterized by expression of exhaustion markers, an altered metabolic profile, and specific transcriptional program. Interestingly, clonal expansion was not organ-specific, as expanded clones were observed in all target organs.
Conclusion Our data underscore the influence of tissue parenchyma on the phenotype and transcriptional program of infiltrating immune cells. Specifically, solid organs (liver and kidney) possess the capacity to suppress T cell responses, potentially limiting self-damage. In contrast, T cells from lymphoid and mucosal tissues (skin and lung) exhibit a more activated phenotype. This dichotomy can be explained by the evolutionary need to minimize immune-mediated damage in solid organs while maintaining effective immunity against external infections in mucosal tissues. By gaining a deeper understanding of how immune cells are modulated within distinct tissue microenvironments, we may identify strategies to selectively target organ-specific manifestations while minimizing systemic immunosuppression.

206 T CELLS AND TISSUE INJURY IN LUPUS

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Tissue injury is a major cause of morbidity and mortality in SLE. Yet, there is limited knowledge of the mechanistic pathways that cause organ damage in lupus. This lack of insight hampers targeted use of current therapeutics and application of those in development. We have identified a T cell effector program associated with tissue damage in lupus nephritis, analogous to programs of effector cell development and function in states of continual antigen stimulation such as cancer and chronic infection. Our data, and by analogy, data from humans and mice with chronic infection and cancer, lead to our hypothesis, that canonical immune effector programs conserved across vertebrate evolution that are operative upon organismal insult, for example in infection or upon cellular transformation, also drive tissue injury in lupus. These programs proceed along an epigenetically regulated pathway that leads to organ injury.

Biomarkers

301 TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH UPADACITINIB RESULTS IN THE COORDINATED INHIBITION OF TYPE 1 IFN-RELATED BIOMARKERS: BIOMARKER ANALYSIS OF THE M19–130 (SLEEK) PHASE 2 STUDY

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Background Activation of Type I interferons (IFNs) and a wide array of innate and adaptive immune mediators are hallmarks of the pathogenesis of systemic lupus erythematosus (SLE) and activation of IFN pathways correlates with disease activity.[1] In a phase 2 study of SLE patients, upadacitinib (UPA, Janus kinase inhibitor) given alone or in combination with elsubrutinib (ABBV-599, Bruton's tyrosine kinase inhibitor) resulted in significant improvement in disease activity as measured by British Isles Lupus Assessment Group-Based Combined Lupus Assessment (BICLA) and SLE Responder Index-4 (SRI-4) at weeks 24 and 48.

Objective To evaluate the impact of UPA and ABBV599 on immunologic pathways associated with SLE pathogenesis

Methods SLE patients (n = 205) were randomized to (placebo [PBO]: n = 75; UPA 30 mg QD: n = 62; ABBV599: n = 68). At screening, patients were stratified by their SLE Disease Activity Index 2000 (SLEDAI- 2K) score, corticosteroid dose (>10-mg prednisone or not), immunosuppressant and IFN score.

Proteomic analyses were performed on the plasma samples using a commercial proximity-extension immunoassay. A repeated mixed linear model was used to compare changes in biomarkers vs PBO and Pearson's correlation was tested to compare protein biomarkers, IFN score, and SLEDAI-2K score. All analyses were corrected for multiple testing using the Benjamini-Hochberg method. Enrichment analyses were performed to elucidate the biological pathways associated with changes in protein biomarkers.

Results As expected, elevated IFN gene expression at baseline was associated with higher SLEDAI 2K disease activity scores, increased anti-double stranded DNA titers, and lower levels of complement components. Expression of serum proteins related to the IFN pathway, such as CXCL10, sialic acid binding immunoglobulin-like lectin 1, IFN gamma, and ZBP1, positively correlated with the IFN score. Treatment with UPA monotherapy or the combination ABBV-599 significantly reduced the IFN gene scores compared with PBO at weeks 4 and 24 ($P \leq .0001$). Proteomic analyses revealed 301 protein biomarkers differentially modulated at weeks 2, 12, and 24 compared with PBO, including significant downregulation of Type I IFN pathway proteins. There were additional impacts of UPA and ABBV-599 on T-cell-associated cytokines, B cells, macrophages, and innate response markers. These effects were similar with UPA and ABBV-599, suggesting that the main effect was attributable to activity of UPA.

Conclusions These results suggest that the clinical benefit demonstrated by UPA in patients with SLE includes the modulation of Type I IFN with impact on several core pathogenic pathways involved in SLE. The main biomarker effects of UPA and ABBV-599 were driven by UPA.

REFERENCE

1. Crow MK. *J Immunol.* 2014;**192**(12):5459–68.

Conflicts of interest MCG, JF, SC, AF, TS are full-time employees of AbbVie and may hold AbbVie stock or stock options. **JTM** has served as a consultant and/or scientific advisor for AbbVie, Alexion, Alumis, Amgen, Astra Zeneca, Aurinia, Bristol Myers Squibb, EMD Serono, Genentech, Gilead, GlaxoSmithKline, Lilly, Merck, Pfizer, Provention, Remegen, Sanofi, UCB, and Zenas, and has received research support from Astra Zeneca, Bristol Myers Squibb, and GlaxoSmithKline.

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302 RESTING STATE FUNCTIONAL CONNECTIVITY IN SLE PATIENTS AND ASSOCIATION WITH COGNITIVE IMPAIRMENT AND BLOOD-BRAIN BARRIER PERMEABILITY

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Objective Cognitive impairment (CI) is the most frequent manifestation of neuropsychiatric systemic lupus erythematosus (NPSLE), yet the mechanisms underlying it remain poorly understood. We have previously reported an association between enhanced permeability of the blood-brain barrier (BBB), loss of grey matter volume and cognitive impairment in SLE patients. This study examined the associations of brain functional connectivity (FC) with CI and BBB dysfunction among patients with SLE.

Methods Cognitive function was assessed by neuropsychological testing (n=77). Resting-state FC (rsFC) between brain regions, measured by functional MRI (n=78), assessed coordinated neural activation in 131 regions across five canonical brain networks. BBB permeability was measured by dynamic contrast-enhanced MRI (DCE-MRI) (n=61). Differences in rsFC were compared between SLE patients with CI (SLE-CI) and those with normal cognition (SLE-NC), between SLE patients with and without extensive BBB leakage, and with healthy controls.

Results A whole-brain rsFC comparison found significant differences in intra-network and inter- network FC in SLE-CI versus SLE-NC patients. The affected connections showed a reduced negative rsFC in SLE-CI compared to SLE-NC and healthy controls. Similarly, a reduced number of brain-wide connections was found in SLE-CI patients compared to SLE-NC (P=0.030) and healthy controls (P=0.006). Specific brain regions had a lower total number of brain-wide connections in association with extensive BBB leakage (P=0.011). Causal mediation analysis revealed that 64% of the association between BBB leakage and CI in SLE patients was mediated by alterations in FC.

Conclusion SLE patients with CI had abnormalities in brain rsFC which accounted for most of the association between extensive BBB leakage and CI.