feron-related proteins, neutrophils, and cell death processes could be driving the inflammatory response in these subgroups. Three different clusters had a predominant T cell signature, which were supported by lymphocyte counts (figure 2).

Conclusion Our data support a diverse molecular profile in CLE that further adds to the clinical variations of this skin disease, and may affect disease course and treatment selection. Future studies with a larger and diverse CLE patient cohort are warranted to confirm these findings.

Cutaneous lupus

LYMPHATIC DYSFUNCTION IN LUPUS CONTRIBUTES TO CUTANEOUS PHOTOSENSITIVITY AND LYMPH NODE B CELL RESPONSES

Patients with systemic lupus erythematosus (SLE) are photosensitive, developing skin inflammation with even ambient ultraviolet radiation (UVR), and this cutaneous photosensitivity can be associated with UVR-induced flares of systemic disease, with increased autoantibodies and further end organ injury.

Mechanistic insight into the link between skin disease and autoimmunity is limited. Signals from skin are transmitted directly to the immune system via lymphatic vessels, and here we show evidence for potentiation of UVR-induced lymphatic flow dysfunction in SLE patients and murine models. Improving lymphatic flow by manual lymphatic drainage (MLD) or with a transgenic model reduces both cutaneous photosensitivity and lymph node B cell responses. Mechanistically, improved flow restrains B cell responses by activating a fibroblastic reticular cell-monocyte axis. Our results point to a lymphatic flow-lymph node stromal axis as a link between photosensitivity and autoimmune responses and as a therapeutic target in lupus, have implications for understanding skin-immune interactions in other diseases such as skin cancer, and suggest the possibility of MLD as an immediately available, cost-effective adjunctive treatment in lupus and related diseases.

PLASMACYTOID DENDRITIC CELLS ARE NOT MAJOR PRODUCERS OF TYPE 1 INTERFERONS IN CUTANEOUS LUPUS

Background Type 1 interferons (IFN-1) are major drivers of disease activity in systemic (SLE) and cutaneous lupus erythematosus (CLE). Plasmacytoid dendritic cells (pDCs) are the major producers of IFN-1 during viral infection. Therefore, pDCs have been hypothesized to be the primary IFN-1
producing cell in lupus. IFN-1 production by pDCs has not been extensively studied due to reliance on interferon gene signatures as a proxy for IFN-1 levels as well as a reliance on pDCs from healthy controls for in vitro studies. However, it has been known that pDCs are reduced in the circulation in SLE and have also been more recently shown to have an exhausted phenotype, suggesting that pathogenic pDCs may be located in the end organs.

Methods Well characterized CLE patients were recruited from a prospective database. We performed imaging mass cytometry on archived treatment naïve CLE skin (n=48) and a subset were also used for mRNA in situ hybridization. Fresh 4mm punch biopsies (n=3) and blood (n=4) were obtained from CLE patients and healthy controls (n=3) for multiplexed flow cytometry or cytometry by time of flight (CyTOF).

Results In lesional CLE skin, only 8.5% (IQR 0.0-22.22) of pDCs were IFNα+ (figure 1A,B). Across all CLE biopsies, pDCs were the second lowest contributor of absolute IFNα+ cells (Median 1; IQR 0-4.5), with B lymphocytes being the smallest contributor. Classic dendritic cells (cDCs) and macrophages (Mφ) were the largest relative and absolute contributors of IFNα in CLE (figure 1C). For IFNβ, only 16.7% of pDCs were positive, compared to 60.7% of CD14+CD16+ Mφ. pDCs were also the second lowest contributors of IFNβ+ cells (Median 1; IQR 0-7), with B lymphocytes again being the lowest (figure 1D). For IFNκ, the largest contributor was CD68 Mac, CD14+CD16+ Mac, and cDCs (figure 1E). IFN-1 mRNA was detected in ITGAX (CD11c) positive cDCs but we did not identify colocalization of pDC- specific gene, CLEC4C (BDCA2), and IFN-1 mRNA (figure 2). Flow cytometry on leukocytes eluted from fresh lesional biopsies showed a median of 5.2% of pDCs were positive for IFNα (IQR 3.85 – 9.64) which was significantly lower than the median of 37.9% of HC PBMC pDCs (34.5 – 39.8) (p<0.0001). In comparison, other leukocytes in CLE skin displayed greater positivity for IFNα such as CD4 T cells (Median, IQR) (24.5%, 10.2 – 29), CD14+ cells (17.6%, 10.7 – 23.1), Classical Monocytes (CD14++CD16-) (11.4%, 10.2 – 20.2), Intermediate Monocytes (CD14++CD16+) (13.7%, 12.4 – 17.5), CD68+ Macrophages (24.6%, 10.9 – 32.4), M1 Macrophages...
Abstract 803 Figure 2  A) Representative images of mRNA in situ hybridization of IFNα and IFNβ mRNA with markers for conventional dendritic cells (ITGAX) and plasmacytoid dendritic cells (CLEC4C). No observable overlap of type 1 interferon mRNA and CLEC4C was seen. B) tSNE plot of PBMCs from a CLE patient stained and acquired by CyTOF. Plasmacytoid dendritic cells, identified principally on CD123 expression, demonstrate little type 1 interferon staining as well as activation of the STING pathway (a signaling molecule upstream of type 1 interferon transcription) on the Z axis.

Abstract 803 Figure 3  Flow cytometry of leukocytes eluted from CLE skin demonstrating significantly fewer IFNα+ plasmacytoid dendritic cells (pDCs) in cutaneous lupus erythematosus (CLE) skin (Median 5.2%, p<0.0001) and peripheral blood mononuclear cells (PBMCs) (12.7%, p<0.0001) than healthy control PBMCs (37.9%). Abbreviations: cDC: classical dendritic cell; pDC: plasmacytoid dendritic cell; moDC: monocyte derived dendritic cell; cM: classical monocyte; intM: intermediate monocyte; ncM: nonclassical monocyte; Mφ: macrophage.
Molecular Biology of Lupus

902 LOSS-OF-FUNCTION VARIANTS IN SAT1 CAUSE X-LINKED CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

Lingxiao Xu1,2†, Jian Zhao1, Qin Sun1, Xue Xu1, Lei Wang1, Ting Liu1, Yunjuan Wu1, Jinfeng Zhu1, Linyu Geng1, Yun Deng1, Alexander Avgulevitch1,2, Diane L Kamen1, Jim C Oates1,2, Priithi Raj3, Edward K Wakeland3, R Hal Scofield4,6, Joel M Guthridge4,6, Judith A James4,6, Bevra H Hahn3, Deborah K McCurdy7, Fang Wang9, Miaoja Zhang1, Wenfeng Tan1, Gary S Gilkeson1, Betty P Tsao1†. Division of Rheumatology, Immunology, and Allergy, Department of Medicine, University of California Los Angeles, Los Angeles, CA, 90095, USA; 2Department of Rheumatology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; 3Department of Rheumatology and Immunology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; 4Arthritis & Clinical Immunology Research Program, Division of Genomics and Data Sciences, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; 5Veterans Affairs Medical Center, Oklahoma City, OK, USA; 6Oklahoma Clinical and Translational Science Institute, University of Oklahoma Health Sciences Center, 920 NE Stanton L. Young, Oklahoma City, OK, USA; 7Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, University of California Los Angeles, Los Angeles, CA, 90095, USA; 8Ralph H. Johnson VA Medical Center, Medical Service, Charleston, SC, USA; 9Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; 10Department of Rheumatology and Immunology, WuXi People’s Hospital, Wuxi, Jiangsu, China; 11Department of Nephrology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; 12Cardiovascular Developmental Biology Center, Department of Regenerative Medicine and Cell Biology, College of Medicine, Children’s Research Institute, Medical University of South Carolina, Charleston, South Carolina, USA; 13Division of Rheumatology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA; *Presenter.

Objectives Families that contain multiple siblings affected with childhood-onset of systemic lupus erythematosus (SLE) likely have strong genetic predispositions. We performed whole-exome sequencing (WES) to identify familial rare risk variants and to assess their effects in lupus.

Methods Sanger sequencing validated the two ultra-rare, predicted pathogenic risk variants discovered by WES and identified additional variants in 562 additional SLE patients. Effects of a splice site variant and a frameshift variant were assessed using a Minigene assay and CRISPR/Cas9-mediated knock-in (KI) mice, respectively.

Results The two familial ultra-rare, predicted loss-of-function (LOF) SAT1 variants exhibited X-linked recessive Mendelian inheritance in two unrelated African-American families. Each LOF variant was transmitted from the heterozygous unaffected mother to her two sons with childhood-onset SLE. The p. Asp40Tyr variant affected a splice donor site causing deleterious proteinuria and elevated expression of type I interferon inducible genes. SAT1 is highly expressed in neutrophils and...