that reduced LC ADAM17 activity in two lupus models contributed to their photosensitivity. Non-lesional human SLE skin also showed evidence of a dysfunctional LC-keratinocyte axis; however, what causes LC dysfunction is not known. Here we test the hypothesis that IFN-I in the skin contributes to LC ADAM17 dysfunction and thus photosensitivity.

Methods To assess IFN-I gene signature, microarray of non-lesional skin from human cutaneous LE and RNA sequencing of whole skin from lupus mouse models were performed. To quantify human and murine LC ADAM17 activity and expression, *in vitro* and *ex vivo* flow cytometric-based assays were conducted. To assay photosensitivity, readouts of skin inflammation and cellular infiltrate were measured and characterized.

Results We show that non-lesional skin from human cutaneous LE and photosensitive MRL/lpr and B6.Sle1yaa mice all share IFN-I signatures and that IFN-I is sufficient to reduce human and murine LC ADAM17 activity independently of surface ADAM17 levels. IFN-I induced LC ADAM17 activity defects were abrogated with tofacitinib, a JAK kinase inhibitor approved for rheumatoid arthritis and other rheumatologic diseases. We further show that anti-IFNAR1 treatment prior to UVR exposure in lupus models restores LC ADAM17 activity and limits photosensitivity.

Conclusions Together, our results suggest a model whereby the elevated IFN-I in non-lesional skin contributes to photosensitivity at least in part by causing LC ADAM17 dysfunction. The corollary is that anti-IFNAR has beneficial effects at least in part by correcting LC ADAM17 dysfunction.

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202 CAUSES OF DEATH AMONG POPULATIONS WITH SYSTEMIC LUPUS ERYTHEMATOSUS BY SEX, RACE AND ETHNICITY

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Background Data indicate that minority populations with systemic lupus erythematosus (SLE) are at higher risk of developing disease and have more severe outcomes, including mortality. However, whether specific causes of death vary by race and ethnicity has largely been unexplored, particularly for Asians and Hispanics.

Methods The California Lupus Surveillance Project identified potential SLE cases using community rheumatology and nephrology clinics, community hospitals, and integrated healthcare systems among individuals who were residents of San Francisco County, CA during January 1, 2007 – December 31, 2009. Cases were matched to the 2007–2017 National Death Index (NDI) data, which included the underlying cause of death for each individual. Chi-squared tests were used to examine differences in underlying cause of death by race (white, Black, Asian), ethnicity (Hispanic, non-Hispanic), and sex. Age-standardized mortality ratios (SMRs) between SLE patients and the general San Francisco county population were calculated for the leading cause of death, and estimated

Abstract 202 Table 1 Standardized mortality ratios of cardiovascular disease (CVD) in SLE patients compared to the general San Francisco county population, age-standardized, 2007–2017

	Total SLE Population	CVD as Underlying Cause of Death		
		Observed CVD Deaths in CLSP	Expected CVD Deaths	SMR (95% CI)
Overall	809	45	12.4	3.63 (2.65, 4.86)
Race				
White	311	13	5.3	2.43 (1.29, 4.16)
Black	164	16	5.5	2.89 (1.65, 4.70)
Asian	294	14	3.7	3.83 (2.09, 6.42)
Ethnicity				
Hispanic	123	7	1.1	6.45 (2.59, 13.29)
Non-Hispanic	604	36	10.6	3.39 (2.37, 4.69)
Sex				
Female	728	40	8.6	4.65 (3.32, 6.34)
Male	81	5	1.4	3.48 (1.13, 8.12)

observed versus expected deaths by sex, race, and Hispanic/Latino ethnicity.

Results During the study period, 135 deaths related to SLE were identified (n=809). The top underlying cause of death overall (33%) and across all racial and ethnic groups was cardiovascular disease (CVD). Other top causes of death included rheumatic disease (18%) and hematological/oncological conditions (18%) overall, and across all racial groups. Analyses examining any cause of death indicated that rheumatic disease was more commonly indicated among white (50%) and Asian (46%) patients as compared to Black (27%) patients with SLE. In comparison to the general population of San Francisco County, CVD as the underlying cause of death was over three times higher among individuals with SLE (SMR=3.63) (table 1). CVD deaths for those with SLE were nearly three times higher for Black, approximately four times higher for Asian, and over six times higher for Hispanic/Latino individuals. CVD deaths were also elevated for females (SMR=4.7) and males (SMR=3.5) with SLE compared to the general population.

Conclusions Our results show that CVD is the leading underlying cause of death among SLE patients across various racial and ethnic groups, and that rheumatic disease may be less likely to be listed as a cause of death among Black patients with SLE. Further, Asian and Hispanic/Latino SLE patients experience a disproportionate burden of CVD mortality compared with the general population.

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203 NON-LESIONAL AND LESIONAL LUPUS SKIN SHARE INFLAMMATORY PHENOTYPES THAT DRIVE ACTIVATION OF CD16+ DCs

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Background Cutaneous lupus erythematosus (CLE) is an often disfiguring autoimmune disease affecting systemic lupus erythematosus (SLE) patients and a roughly similar number of CLE-only patients without systemic disease. Effective therapies for CLE are limited, and additional studies are needed to better understand the cellular composition and mediators of CLE pathology in order to improve treatment modalities.

Methods Lesional and non-lesional skin biopsies and peripheral blood mononuclear cells (PBMCs) from 7 patients with active CLE lesions and 14 healthy control skin biopsies were subjected to scRNA-seq on the 10X platform. Cells were clustered using Seurat and annotated according to putative cell type-specific markers. Keratinocytes (KCs), fibroblasts (FBs), T cells, and myeloid cells were sub-clustered and cell subsets annotated. Cytokine signatures were generated by treating KCs and FBs with panels of cytokines and identifying induced genes. For KC and FB sub-clustering analyses, each cell was scored for each cytokine signature. Cell-cell communication was examined using CellPhoneDB to perform ligand-receptor analysis for cell types. To further investigate cellular interactions, imaging mass cytometry and spatial transcriptomics were performed, and cell signatures derived from scRNA-seq were used to plot the proximity of different cell types in discoid lupus lesions. Finally, myeloid cells were identified from skin and PBMC samples and subclustered. Pseudotime analysis was performed on cells bridging the connection between circulating and skin-resident myeloid cells.

Results Both lesional and non-lesional SLE/CLE KCs exhibited strong type I interferon scores. Lesional and nonlesional SLE/CLE skin exhibited dramatic shifts in cell-cell crosstalk; CD16+ DCs were highly enriched in CLE lesions relative to control and were among the most active communicators as expressers of both ligands and receptors. Spatial transcriptomics demonstrated CD16+ DCs localizing most prominently in the superficial dermis, enabling interaction with KCs. This was confirmed using imaging mass cytometry. Pseudotime analysis of paired circulating and skin myeloid cells revealed CD16+ DCs may arise from non-classical monocytes, with discrete shifts in myeloid cell transcriptional states, including a robust IFN education in the skin, detectable across this transition.

Conclusions Non-lesional skin of patients with SLE and CLE exists in a type I IFN-rich, 'prelesional' state. This affects gene transcription in all major skin cell types and dramatically alters cell-cell communication. Non-classical monocytes may infiltrate this environment to become CD16+ DCs that engage in crosstalk with diverse cell types as one of the earliest steps in the evolution of CLE.

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THE ROLE OF NEUTROPHILS IN THE CLINICAL SEVERITY OF LUPUS NEPHRITIS PATIENTS WITH CONCURRENT SKIN DISEASE

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Background Skin disease affects >80% of lupus patients and has been linked to lupus nephritis (LN) flares. We recently found that skin inflammation caused by ultraviolet light leads to increased expression of renal inflammatory and injury markers as well as proteinuria, mediated by neutrophils, which migrated from the inflamed skin to the kidneys. These data

prompted the hypothesis that presence of concurrent skin disease in lupus patients leads to worse nephritis mediated by neutrophils.

Methods Lupus nephritis biopsies (n=43) were retrieved from the Dartmouth Hitchcock Medical Center tissue bank and grouped: (i) LN with concurrent skin rash (malar, subacute, or discoid n =15) and (ii) LN without any rash (n=6) at the time of LN diagnosis (class IV). Patients with inconclusive or incomplete skin findings were excluded. The study included only female patients. Clinical and laboratory data (absolute neutrophil (ANC) and lymphocyte (ALC) counts, serum creatinine, glomerular filtration rate (GFR), autoantibody titers, and complement) were collected by chart review. Histologic and immunofluorescence data were extracted from biopsy reports. Student's t-test was performed to detect statistical significance between patient groups.

Results Presence of skin rash at the time of LN flare was indicative of more active disease, reflected by higher ANA, anti-dsDNA IgG, and low C3 and C4 levels. LN patients with concurrent skin disease had a higher neutrophil count ($p < 0.05$) and neutrophil-lymphocyte ratio ($p < 0.01$), but not ALC, compared to LN patients without a concurrent skin rash. High neutrophil counts in the presence of skin disease associated with lower GFR (< 60 ; $p < 0.01$). This association was not seen in the absence of concurrent skin disease and rash alone did not predict GFR. Analysis of kidney immunofluorescence revealed that concurrent skin disease at the time of LN flare associated with greater IgA deposition. Increased renal IgA levels associated with higher neutrophil but not lymphocyte counts ($p < 0.01$). This was specific to IgA as no associations with IgG or IgM deposition were detected.

Conclusions Our study provides novel findings that suggest neutrophils may be the pathogenic link between skin inflammation and LN: (i) higher neutrophil counts are found in the presence of a skin rash at the time of LN flare, (ii) neutrophilia but not lymphocytosis in the presence of a skin rash associates with worse kidney function, and (iii) high neutrophils in the presence of skin rash associate with increased renal IgA. These data provide a novel model of IgA-driven activation of neutrophils leading to kidney injury initiated by skin inflammation.

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LYMPHATIC DYSFUNCTION IN LUPUS PHOTOSENSITIVITY

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Background The lymphatic system is composed of vessels which carry fluid, soluble molecules, and cells from peripheral tissue to draining lymph nodes. Photosensitivity, an exaggerated inflammatory response in response to ultraviolet radiation (UVR), is present in most patients with Systemic Lupus Erythematosus (SLE). Lymphatic dysfunction has been shown to induce photosensitivity in wild-type models, thus we