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