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Evaluating CXCR6 and its ligand CXCL16 as biomarkers for lupus organ involvement: a mini review and brief research report

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Cutaneous lupus erythematosus (CLE) is a group of skin disorders where the immune system attacks skin cells. CLE can affect people who have systemic lupus erythematosus, or can occur independently. In prior studies, CXCL16 and its primary receptor, CXCR6, have been shown to be elevated at the RNA or protein level in different organs that are affected by lupus. In this systematic review, we sought to understand whether CXCR6 and its ligand CXCL16 could serve as biomarkers for lupus skin or other organ involvement. Our search strategy and protocol are registered on Prospero under # CRD42024583076. CXCL16 was shown to be a biomarker of lupus nephritis and disease activity in both urine and serum samples in multiple studies. CXCL16 was also elevated in cerebrospinal fluid in neuropsychiatric lupus patients as well as other autoimmune brain conditions. Last, we queried publicly available datasets and our own datasets to evaluate expression of CXCR6 and CXCL16 in lupus skin. CXCR6 but not CXCL16 was enriched in lupus skin across multiple datasets and model organisms. Taken together, our study corroborates the CXCR6 chemokine family as a potential biomarker of lupus organ involvement.

KEYWORDS

lupus, CXCR6, CXCL16, plasma, urine, cerebrospinal fluid (CSF), skin

Introduction

Cutaneous lupus erythematosus (CLE) is a spectrum of autoimmune skin disorders that may occur independently or as part of systemic lupus erythematosus (SLE). CLE has manifestations of autoimmunity with complex pathophysiology involving dysregulated inflammatory signaling and aberrant immune cell trafficking. Chemokines play a critical role in organizing immune cell migration to sites of inflammation, with emerging evidence suggesting particular importance for the CXCR6-CXCL16 axis in immune-mediated skin diseases. This chemokine pathway may represent a fundamental mechanism underlying both the initiation and persistence of inflammatory skin lesions in lupus. Recent cross-species investigations have revealed intriguing patterns of conservation, suggesting evolutionary significance and potential therapeutic relevance of this pathway (1). Our research has focused on elucidating the specific contributions of the CXCR6-CXCL16 interaction in lupus pathogenesis, with particular attention to its role in tissue-resident memory T cell populations.

In juvenile SLE patients, the chemokine CXCL16, which is a ligand for CXCR6, was elevated in recent studies. CXCL16's expression in these patients was associated with clinical features such as alopecia, malar rash, and nephritis (2). CXCL16 is produced by keratinocytes (2, 3), and its expression is induced by TLR7 activation (4) which is a key signaling pathway implicated in both the CLE murine model used in our studies (5) and in human lupus (6, 7). It is also upregulated by ultraviolet (UV) light (3, 4), which suggests a potential role in photosensitivity, a hallmark of cutaneous lupus. CXCL16 has also been associated with Th1:Th2 imbalances in patient with autoimmune thrombocytopenia (8), a pattern that matches our own observations of T helper cell plasticity in murine CLE (9). Two independent studies have demonstrated that CXCR6 is expressed on CD8⁺ tissue-resident memory T cells (Trm) within the tumor microenvironment (10, 11), highlighting a potential role for the CXCL16-CXCR6 axis in Trm cell biology.

Building on these findings, we performed a systematic review of CXCL16-CXCR6 as potential biomarkers of lupus, which we present here. CXCL16 appears to be a promising biomarker of lupus nephritis. We also queried publicly available mouse, human, and canine CLE datasets (4–6) and found that CXCL16 upregulation in cutaneous lupus lesions is conserved across all three species. Interestingly, CXCL16 was lower in established CLE patients assessed by tape stripping, which we hypothesize may be due to sun avoidance and/or current treatment status. This cross-species conservation, combined with the role CXCL16 plays in immune signaling and Trm cell maintenance, identifies it as a promising biomarker and potential therapeutic target in lupus.

Methods

Systematic review

Search strategy

Our search strategy and protocol are registered on Prospero under # CRD42024583076. A comprehensive literature search was conducted by a medical librarian on August 22, 2023, using the following bibliographic databases from inception: Ovid MEDLINE® (ALL-1946 to Present); Cochrane Library (Wiley); PubMed (NIH) and Scopus (Elsevier). We used controlled vocabulary for both *lupus and *CXCL16/CXCR6. The entire search strategy is available in [Supplementary Table S1](#).

Eligibility criteria

Eligibility criteria were as follows: 1. studies involving lupus erythematosus; 2. studies measuring CXCL16 and/or CXCR6 as biomarkers. Exclusion criteria included: 1. studies of diseases that were not lupus; 2. studies that did not include measurements of CXCR6 and/or CXCL16; and 3. studies in a language other than English. We allowed any article types that presented primary data to be included, including randomized control trials, non-randomized experimental studies, case-control studies, cohort studies, cross-sectional studies, comparative studies, systematic

reviews, observational studies, prevalence studies, open-label trials, *in vitro* experiments, and *ex vivo* studies. We also included both human and murine studies.

Exclusion criteria for full-text review included the following:

1. duplicate article; 2. did not study lupus; 3. did not measure CXCR6/CXCL16; 4. full article not available in all libraries for interlibrary loan request; 5. full text not in English. Review articles, editorials, and text/opinion pieces were also excluded in the full-text review with the rationale that they would have summarized the same primary literature studies.

Methodological quality assessment

We assessed the risk of bias using the ROBINS-I tool with the following domains: bias due to missing data, bias due to deviations from intended interventions/studies, bias in selection of participants, bias in classes of interventions, bias in measurement of outcomes, bias in selection of reported results, risk of bias due to confounding.

Data extraction

Our data extraction template included the following entries for reviewers to complete: 1. study ID; 2. title; 3. country in which the study was conducted; 4. notes; 5. aim or objective of the study; 6. study design (e.g., randomized clinical trial, case report, etc.); 7. publication date; 8. study funding sources; 9. possible conflicts of interests for study authors; 10. participants—population description (mice, humans, cell lines, etc.); 11. inclusion criteria; 12. exclusion criteria; 13. the total number of participants; 14. total number of experimental repeats; 15. plants/compounds/extracts tested; 16. active ingredients tested (if known); 17. controls used (e.g., vehicle, positive controls, negative controls, etc.); 18. primary outcome—cutaneous findings—Was the treatment efficacious (yes/no)? Statistically significant (yes/no)? 19. primary outcome—inflammation—Was the treatment efficacious (yes/no)? Statistically significant (yes/no)? 20. Primary outcome—other organ systems (e.g., kidney, brain, etc.). Was the treatment efficacious (yes/no)? Statistically significant (yes/no)? Forest plots of study outcomes were generated using GraphPad Prism software.

Primary data analysis

Patient samples

We queried our dataset of archival skin biopsies from CLE patients seen at Howard University Hospital for CXCR6/CXCL16 gene expression (1). Briefly, samples were obtained through an archival tissue IRB protocol with Memorandum of Understanding (UMass Chan & Howard University IRBs). Disease status was confirmed by chart review by a board-certified dermatologist (CF).

Microarray and statistical analysis

We used nSolver software to generate normalized gene expression counts from the NanoString myeloid v2 probeset. Samples with QC flags were excluded (1 healthy sample).

Normalized gene counts were analyzed with student's *t* test and Receiver operator characteristic (ROC) curve functions using GraphPad Prism software v 10.

Dataset reanalysis and statistics

We queried publicly available datasets for *CXCR6/CXCL16* expression using Geo2R software. These included human data from Scholtissek et al. GSE95474 (13), Yildiz-Altay et al. (1), and Seremet, Domizio et al. GSE193068 (14, 15); mouse data from Mande et al. (6); and canine data from Garelli & Wong and Amudzi et al. (16, 17). Normalized count values were plotted in GraphPad Prism software v 10. Each dataset was assessed for normality before selection of statistical tests, with normally distributed data employing *t* tests and non-normally distributed data employing Mann-Whitney *U* tests. Directional hypothesis testing for one-tailed results was to test the hypothesis that *CXCR6/CXCL16* were higher in lupus than controls, which was based on our observations from the Balb/c mouse model and published studies.

Results

Following our search strategy, we identified 103 eligible studies from SCOPUS, Ovid MEDLINE, PubMed and Cochrane library. 35 duplicates were removed, leaving 68 studies for screening. Of these, 49 were irrelevant. 19 full-text studies were assessed, 8 of which were excluded. Reasons for exclusion included wrong outcomes ($n = 1$), wrong comparator ($n = 2$), wrong study design ($n = 3$) and review article with no primary data ($n = 1$). This search is also summarized in Figure 1. Of the 11 studies included, most used a prospective cohort design on human biological samples including serum, urine, and kidney biopsies. All of these studies

noted significant increases in *CXCL16* or its receptor *CXCR6* (summarized in Table 1).

Systematic review results

Wu et al. (18) examined urinary biomarkers in lupus nephritis using both murine models and human patient samples. Researchers analyzed the urine of lupus-prone mice and SLE patients for VCAM-1, P-selectin, TNFR-1, and *CXCL16*, finding significantly elevated levels in those with active nephritis. These markers correlated with disease severity and were primarily derived from the kidney rather than the bloodstream. Immunohistochemical analysis confirmed their presence in inflamed renal tissues, particularly in endothelial and tubular cells. In human SLE patients, urinary levels of these biomarkers distinguished those with nephritis from non-nephritic individuals with high sensitivity and specificity. VCAM-1 and P-selectin, both involved in inflammation, were particularly enriched in lupus kidneys and urine, while TNFR-1 and *CXCL16* were newly identified as urinary biomarkers. The findings suggest these molecules play roles in disease pathogenesis while serving as potential noninvasive diagnostic tools. Their detection in urine provides a more accessible way to monitor disease progression without the need for invasive kidney biopsies.

Qin et al. (19) investigated serum soluble *CXCL16* (s*CXCL16*) levels in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and compared these levels to healthy controls. A total of 47 serum samples were collected from 35 SLE patients, with 12 patients providing samples before and after treatment with glucocorticoids and immunosuppressants. The results showed that serum s*CXCL16* levels were significantly higher in SLE patients compared to RA patients and healthy controls. The study also found that s*CXCL16* levels correlated with disease activity in SLE, as indicated by SLE Disease Activity

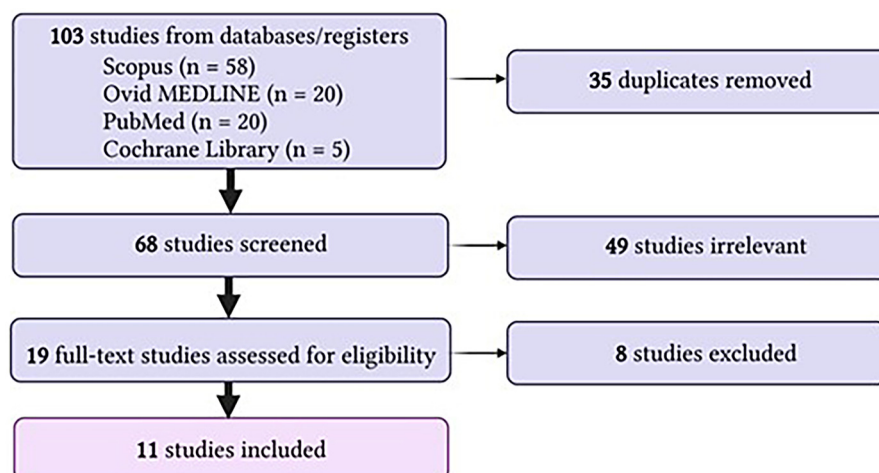


FIGURE 1
PRISMA diagram of systematic review assessing *CXCR6/CXCL16* as biomarkers in lupus.

TABLE 1 Summary of systematic review findings for CXCR6/CXCL16 biomarkers in lupus studies.

Study	Author/ year	Country	Type of Study	Organism (Human/ Mouse)	Number	Specimen	Level of CXCR6 and/or CXCL16	Overall risk of bias judgement:	Overall risk of bias judgement: supporting text
1	Qin 2014	China	Prospective cohort study	Human	47 serum samples was obtained from 35 SLEpatients. From 12 of the patients, serum samples were collect-ed twice	Serum	CXCL16 SLE patients $2.41 \pm 0.16 \mu\text{g/L}$, $n = 35$; healthy donors mean $\pm$ SEM, $1.37 \pm 0.08 \mu\text{g/L}$, $n = 15$; $P < 0.0001$	Low	Patient data is readily available in the manuscript. Authors assess the relationship of the CXCL16 levels with disease activity and organ damage.
2	Ayyappan 2019	United States	Prospective cohort study	Human	30 SLE & 30 healthy	Serum	CXCL16 males: $\sim 12.5 \text{ ng/ml}$ SLE vs. 10 ng/ml healthy ($p = 0.002$); females: $\sim 11 \text{ ng/ml}$ SLE vs. $\sim 12 \text{ ng/ml}$ healthy ($p = 0.081$)	Low	The cohort study by Ayyappan et al. demonstrates low risk of bias, with robust methodology including standardized laboratory techniques, carefully matched controls, and comprehensive reporting of both significant and non-significant findings.
3	Singh 2012	United States	Prospective cohort study	Human	74 lupus nephritis patients & 13 healthy volunteers. 24 patients had a concomitant kidney biopsy	Urine & kidney biopsy	CXCL16 mean $24.8 \pm 6.19 \text{ pg/mg}$; $r = 0.24$, $P = 0.02$ for correlation with proteinuria	Low	The cohort study by Singh et al. demonstrates low risk of bias, with clearly defined patient populations, standardized biomarker measurements, and particularly strong validation through concurrent renal biopsies that directly correlate urinary VCAM-1 levels with renal pathology activity.
4	Wen 2018	China	Prospective cohort study	Human	50 SLE, 35 with LN 15 without LN, mean age, 39.2 ± 17.3 years; age range, 18–68 years)	Serum, urine and kidney biopsy	CXCL16 SLE $4.18 \pm 1.59 \text{ ug/ml}$ vs. healthy $2.07 \pm 0.49 \text{ ug/ml}$; $p < 0.001$	Low	The cross-sectional study by Wen et al. demonstrates low to moderate risk of bias, primarily due to lack of multivariate analysis to adjust for potential confounders and absence of blinding in biomarker measurements. While the study has methodological strengths including well-defined participant classification and complete data reporting, the relatively small sample size and potential for selective reporting limit the robustness of the findings regarding CXCL16 and other biomarkers in lupus nephritis.
5	LeBlanc 2006	Netherlands	Prospective cohort study	Human	11 NPSLE, 45 controls (MS and other neuroinflammatory)	CSF & serum	CXCL16 levels in CSF and serum, respectively, were (mean $\pm$ S.D.) $15,503 \pm 1,762 \text{ pg/ml}$ vs. $9,153 \pm 1,571 \text{ pg/ml}$ ($p = 0.01$) for SLE patients and $10,700 \pm 939 \text{ pg/ml}$ vs. $7,270 \pm 723 \text{ pg/ml}$ ($p = 0.006$) for MS patients. Patients with viral meningitis had mean CXCL16 levels of $10,410 \pm 995 \text{ pg/ml}$ vs. $6,975 \pm 1,890 \text{ pg/ml}$ ($p = 0.25$). In bacterial meningitis, CXCL16 was $14,799 \pm 1,132 \text{ pg/ml}$ vs. $9,705 \pm 1,042 \text{ pg/ml}$ ($p = 0.063$). Finally, CSF and serum CXCL16 levels of healthy individuals were $6,000 \pm 971 \text{ pg/ml}$ vs. $2,881 \pm 177 \text{ pg/ml}$, respectively ($p = 0.001$). Although CXCL16 levels in	Moderate	The cohort study by le Blanc et al. demonstrates moderate risk of bias, primarily due to potential confounding factors (medication use, disease duration) and the absence of blinding information in biomarker measurements. While the study has methodological strengths including standardized ELISA techniques and internal controls for assay variability, the relatively small sample sizes in some disease subgroups and limited reporting of demographic characteristics limit the robustness of the findings regarding CXCL16 in cerebrospinal fluid.

(Continued)

TABLE 1 Continued

Study	Author/ year	Country	Type of Study	Organism (Human/ Mouse)	Number	Specimen	Level of CXCR6 and/or CXCL16	Overall risk of bias judgement:	Overall risk of bias judgement: supporting text
							CSF and serum tended to be highest in SLE patients, this difference was only significant for MS ($p = 0.002$)		
6	El-Gamasy 2018	Egypt	Cross-sectional	Human	80 SLE & 60 healthy	Urine	CXCL16 SLE $1,067 \pm 367$ ug/L; healthy 471 ± 106 ug/L, $p < 0.001$	Low	The overall risk of bias in the study is low. The researchers used a cross-sectional design with clearly defined inclusion criteria, appropriate controls, and validated outcome measures (uNGAL, CXCL16, renal biopsy, and SLEDAI), although the small sample size limited statistical power for analyzing biomarker validity across all LN classes.
7	Klocke 2017	Germany	Prospective cohort study	Human	16 patients with active LN, 41 SLE patients with past renal involvement ("past RI") and 37 patients without any renal involvement ("no RI").	Urine	Active LN 15.64pg/mg creatinine, other SLE 0.172 pg/mg creatinine	Moderate	While the study included patient groups and chemokine and receptor profiling, high individual variability in urinary chemokine levels and the lack of a universally predictive biomarker may introduce inconsistency.
8	Hassan 2018	Egypt	Prospective cohort study	Human	27 patients with jSLE (mean age $12.35 \text{ years} \pm 2.26\text{SD}$) in addition to 30 age- and sex-matched healthy controls	Serum	jSLE 10.3 ± 3.27 ug/L, healthy 4.58 ± 1.12 ug/L, $p < 0.001$	Low	The study used a well-defined patient group and matched controls, applied standardized diagnostic and laboratory criteria, and employed validated measures like SLEDAI and ELISA for sCXCL16 levels, although the small sample size and lack of longitudinal follow-up may limit generalizability.
9	An 2021	South Korea	Prospective cohort study	Mouse	8 mice/group	Mouse kidney	CXCL16 copies/GAPDH lupus ~ 4 , healthy ~ 1 , $p < 0.001$	Low	The study used both human samples and well-characterized mouse models with appropriate controls (including NKT-deficient mice), and results were corroborated using multiple experimental approaches, such as flow cytometry, RT-PCR, immunohistochemistry, and cytokine assays. Additionally, the investigators implemented blinded assessments of histopathology and followed ethical guidelines for both human and animal subjects, minimizing risk of bias across key domains.
10	Wu 2007	United States	Prospective cohort study	Mouse & Human	38 SLE, 12 are normal controls; 5 mice/group	Urine	Mouse: $\sim 500\text{--}1,000$ pg over 24 h vs. WT 250 pg over 24 h; Human: 154 vs. 85 pg/mM CXCL16/creatinine, $p = 0.04$	Low	The study minimized bias by including multiple lupus-prone mouse models, well-matched controls, and using standardized ELISA-based quantification with blinded group comparisons. Human subject data were collected under IRB-approved protocols with clear stratification by disease activity, and findings were validated through multiple complementary assays and statistical methods.

(Continued)

TABLE 1 Continued

Study	Author/ year	Country	Type of Study	Organism (Human/ Mouse)	Number	Specimen	Level of CXCR6 and/or CXCL16	Overall risk of bias judgement:	Overall risk of bias judgement: supporting text
11	Ko 2021	United States	Retrospective cohort study	Human	16 CLE & 10 healthy skin; 14 LN & 7 control kidney biopsies	Skin & Kidney archival biopsies	Skin: CXCR6 CLE 3,000–4,000 normalized counts vs. 1,000 healthy normalized counts, Kidney: CXCR6 LN 1,500 normalized counts vs. 250 normalized counts control kidney	Moderate	Although the study used gene expression profiling and well-established statistical methods, it relied on archival, formalin-fixed samples from a wide date range (1997–2011), which may introduce variability in tissue quality and storage conditions. Additionally, outlier samples were removed.

Index (SLEDAI) scores, and were higher in patients with active disease flare-ups. Furthermore, the levels of sCXCL16 were linked to organ damage, specifically in patients with lupus nephritis and cutaneous involvement, suggesting that elevated sCXCL16 could serve as a marker for these conditions. Following treatment, sCXCL16 levels decreased, reflecting improvements in disease activity, although there was no significant change in chronic organ damage. The findings also suggested that sCXCL16 might help monitor disease progression and guide treatment decisions in SLE patients. The study concluded that sCXCL16 could be a useful biomarker for assessing disease activity and organ involvement, particularly in the skin and kidneys, in SLE.

Ayyappan et al. (20) analyzed changes in various immune markers in patients with systemic lupus erythematosus (SLE). The study included 30 SLE patients and 30 age- and gender-matched healthy controls, with comprehensive exclusion criteria ensuring the exclusion of those with recent infections or steroid use. It found that soluble CD14 (sCD14) levels were significantly elevated in SLE patients, with a positive correlation between sCD14 levels and disease activity, indicating a potential role for endotoxemia in SLE progression. EndoCab IgM levels were reduced in SLE patients, suggesting that lower endotoxin neutralization might contribute to elevated sCD14. Additionally, increased levels of lysozyme were found in SLE patients, and lysozyme correlated positively with sCD14, LBP, and FABP2, suggesting a shared stimulus for these immune factors. CXCL16 levels were also elevated in SLE patients and correlated with sCD14, supporting the idea of bacterial exposure influencing these immune responses. The study noted no significant changes in galectin-3 levels in SLE patients, though a positive correlation with sCD14 and lysozyme was observed. Immunosuppressive treatments were found to reduce EndoCab IgM levels but did not affect the ratios of EndoCabs to total immunoglobulins.

Singh et al. (21) investigated the potential of urinary biomarkers, specifically VCAM-1, MCP-1, and CXCL16, in monitoring lupus nephritis (LN) activity and chronicity. The study involved 74 LN patients, 13 healthy volunteers, and 22 disease controls, with a focus on urinary biomarker levels before initiating any new immunosuppressive therapy. It was found that urinary VCAM-1 and MCP-1 levels were significantly elevated in patients with active renal disease, correlating strongly with disease activity scores and 24-h proteinuria. VCAM-1, in particular, was a strong discriminator of active renal disease and was most elevated in patients with class IV LN, which has a poor prognosis. The study also showed that VCAM-1 levels correlated positively with the acute inflammation index (AI), a measure of kidney inflammation, while negatively correlating with the chronicity index (CI), indicating its role in reflecting inflammation and potential reversibility of kidney damage. Interestingly, while VCAM-1 was not specific to LN and was elevated in other types of nephritis, it appeared to be a useful marker for renal injury. The results suggested that urinary VCAM-1 could serve as a valuable marker for monitoring disease activity and potentially predicting kidney damage in LN.

Wen et al. (22) investigated the potential role of IFN- γ , CXCL16, and suPAR as biomarkers in systemic lupus erythematosus (SLE)

and lupus nephritis (LN). Fifty SLE patients were divided into LN and non-LN groups, alongside 15 healthy controls, and their serum, urine, and renal tissue samples were analyzed. The results showed that serum and urine levels of IFN- γ , CXCL16, and suPAR were significantly elevated in SLE patients, particularly in those with LN, and correlated with disease activity indicators such as SLEDAI scores and 24-h proteinuria. Immunohistochemical analysis revealed increased expression of these biomarkers in renal tissues of LN patients, further linking them to kidney inflammation and damage. Strong correlations were observed between serum and urine levels of these markers, suggesting their potential as non-invasive indicators of renal involvement in SLE. Additionally, suPAR showed the strongest association with disease severity, particularly proteinuria, highlighting its potential as a key predictor of renal damage. These findings suggest that IFN- γ , CXCL16, and suPAR interact in the pathogenesis of SLE, likely contributing to local inflammation and systemic disease progression.

le Blanc et al. (23) studied the role of chemokines (CK) in T cell migration into the central nervous system (CNS) during inflammatory conditions. The researchers found that CXCL16 levels were significantly higher in cerebrospinal fluid (CSF) compared to serum, whereas CCL17 and CCL18 were absent in CSF. Elevated CXCL16 was observed in inflammatory conditions such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), and meningitis. Microglia and astrocytes are likely responsible for CXCL16 production, and its increased presence may facilitate immune cell interactions and inflammation. The study also confirmed that CCL18 was elevated in SLE serum but absent in CSF, supporting its role in attracting naïve T cells outside the CNS. The findings suggest that CXCL16 contributes to neuroinflammation by promoting the influx of activated T cells, particularly when the blood-brain barrier (BBB) is compromised. The researchers highlight that CXCL16's role is not limited to neuroinflammatory diseases, as similar mechanisms were observed in rheumatoid arthritis.

El-Gamasy et al. (24) aimed to evaluate urinary neutrophil gelatinase-associated lipocalin (uNGAL) and CXCL16 levels in children and adolescents with systemic lupus erythematosus (SLE) and their role in diagnosing lupus nephritis (LN). A total of 80 SLE patients and 60 age- and sex-matched healthy controls were included, with disease activity assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and renal biopsies performed at initial diagnosis. Urinary uNGAL and CXCL16 levels were measured using enzyme-linked immunosorbent assays (ELISA), and statistical analyses were conducted to assess their diagnostic accuracy. The study found significantly higher levels of uNGAL (8.9 ± 3.56 ng/dl) and urinary CXCL16 ($1,067 \pm 367$ μ g/L) in SLE patients compared to controls ($P < 0.05$). uNGAL showed a stronger correlation with 24-h urinary protein levels ($r = 0.732$) and SLEDAI scores ($r = 0.359$) than CXCL16, indicating its higher diagnostic value. The sensitivity and specificity of uNGAL in predicting LN were 95% and 90%, respectively, making it a more reliable biomarker than CXCL16. Both biomarkers were found to increase with LN severity, with the highest levels observed in Class IV LN, which is associated with worse outcomes. The findings support the use of uNGAL as a potential early predictor of LN progression, aiding in disease monitoring and treatment decisions.

However, the study's limitations include the small sample size and the inability to establish specific cutoff values for different LN classes. Overall, uNGAL and CXCL16 are valuable indicators of LN activity, with uNGAL demonstrating superior diagnostic accuracy.

Klocke et al. (25) investigated the role of chemokines and their receptors in the recruitment of inflammatory cells into the kidneys of lupus nephritis (LN) patients and their potential as biomarkers. The study demonstrated that T cells and macrophages infiltrate the renal interstitium and that specific chemokines such as CCL2, CCL3-5, CXCL10, and CXCL16 play a key role in disease activity. Urine analysis revealed distinct chemokine profiles in active LN patients, with significant differences from serum levels, highlighting their potential as non-invasive biomarkers. Chemokines correlated with disease severity and urinary T-cell and macrophage counts, particularly CXCR3 ligands like CXCL10, which showed strong correlations with CD4+ T-cell levels. The study also identified that CD4+ T cells exhibit diverse chemokine receptor expressions (CCR5, CXCR3, CCR4, CCR6, CXCR6), whereas CD8+ T cells mainly rely on CCR1, CCR5, and CXCR3 for recruitment. Macrophage recruitment appeared to be driven by the CCR2 axis, with elevated CCL2, CCL7, and CCL8 levels in active LN patients. Individual variability in chemokine expression was observed, suggesting that different LN patients may have distinct chemokine recruitment pathways. Urinary chemokine concentrations did not correlate with serum levels, supporting their kidney-specific role. The study provides new insights into leukocyte migration in LN, aligning with findings from rodent models and previous human studies. These findings highlight potential therapeutic targets and reinforce urinary chemokine profiling as a promising diagnostic tool for LN.

Hassan et al. (2) investigated serum sCXCL16 levels in juvenile systemic lupus erythematosus (jSLE) patients and its correlation with disease activity, particularly lupus nephritis. It included 27 Egyptian children with jSLE diagnosed using ACR criteria and 30 healthy, age- and sex-matched controls. Clinical symptoms, laboratory tests, and renal biopsies were performed to assess disease severity, with disease activity classified using the SLEDAI score. Serum sCXCL16 levels were significantly higher in jSLE patients than in controls and correlated positively with lupus nephritis severity, SLEDAI score, anti-dsDNA levels, ESR, and blood pressure. A strong association was observed between sCXCL16 levels and specific cutaneous manifestations, particularly alopecia and malar rash. Patients with more advanced lupus nephritis (class III and IV) had significantly elevated sCXCL16 levels, suggesting its role in disease progression. The study found a negative correlation between sCXCL16 levels and C3, highlighting its potential as a biomarker for disease activity. The findings align with previous studies on the inflammatory role of CXCL16 in lupus nephritis and its association with renal damage. The study suggests that sCXCL16 could serve as a non-invasive marker for monitoring renal involvement in jSLE, reducing the need for repeated renal biopsies. Future therapeutic strategies targeting sCXCL16 could be explored to manage active disease flares and prevent renal complications in jSLE patients.

An et al. (26) studied the role of IL-17-secreting invariant natural killer T (iNKT) cells in lupus nephritis (LN). They found

that patients with LN had significantly higher proportions of IL-17-producing NKT cells in peripheral blood mononuclear cells (PBMCs) and increased IL-17 expression in kidney tissues compared to control groups. Using an experimental autoimmune lupus nephritis (eALN) mouse model, researchers observed that NKT cell-deficient mice had less severe disease progression, lower proteinuria, and reduced renal damage than wild-type mice. The absence of NKT cells led to decreased glomerular immune cell infiltration, lower IL-17 and proinflammatory cytokine expression, and increased levels of IL-27, which inhibits Th17 differentiation. Experiments demonstrated that NKT cells contribute to systemic inflammation and IL-17 production, promoting mesangial cell proliferation and disease progression. *in vitro* studies confirmed that activated NKT cells induced IL-17 secretion, which was diminished upon IL-17 blockade, reducing mesangial cell proliferation. NK1.1+ NKT cells were identified as primary regulators of IL-17 production, with their activation upregulating IL-6, STAT3, and CXCL16 expression, further linking them to LN pathogenesis. A pristane-induced lupus model reinforced these findings, showing that disease severity correlated with IL-17 and NKT cell activation. Blocking IL-17 or depleting NKT cells reduced inflammation and kidney damage, suggesting that IL-17-secreting iNKT cells are central to LN progression. These findings highlight the potential therapeutic targeting of the IL-17/NKT cell axis to mitigate LN severity.

Ko et al. (27) examined gene expression profiles in cutaneous lupus and lupus nephritis to understand their distinct clinical and histological features. Researchers analyzed 16 cutaneous lupus samples (SCLE and CCLE) and 10 normal skin samples, revealing that while lupus skin samples are distinct from normal skin, SCLE and CCLE share highly similar gene expression profiles. Despite clear clinical differences, broad gene expression analysis does not explain these distinctions, suggesting that subtle genetic variations or tissue-specific inflammation may contribute. The study identified a strong type I interferon (IFN) signature in cutaneous lupus, with upregulated genes such as *IFI6*, *IFI44l*, and *CXCL10*, which play key roles in inflammation and immune response. In contrast, lupus nephritis samples showed distinct

gene expression patterns, including increased levels of *CCL19* and *TNFRSF11B*, which are associated with kidney inflammation and damage. The data suggest that cutaneous lupus is characterized by strong immune activation, particularly involving T-cell chemokines and type I IFN pathways, whereas lupus nephritis exhibits a more wound-healing and fibrotic response. Using CIBERSORT analysis, the study found that cutaneous lupus had a predominance of activated CD4+ T cells, whereas lupus nephritis showed more resting memory T cells and M2 macrophages, supporting different immune mechanisms. The study proposes that lupus nephritis may result from immune complex deposition originating from inflammation in distant tissues, such as the skin. Despite similarities in early histological presentation, cutaneous lupus and lupus nephritis follow different immune response pathways, emphasizing the complexity of lupus pathogenesis. These findings provide new insights into lupus biology and may help refine diagnostic and therapeutic approaches for different lupus subtypes. A summary of the findings of these studies is presented in the forest plot in Figure 2.

Evaluating CXCR6/CXCL16 expression in archival skin biopsies

We queried our mouse (1, 6), canine (16, 17) and human (1) CLE transcriptomics datasets to assess *CXCR6/CXCL16* expression in skin, and compared these to other publicly available human datasets GSE95474 from Scholtissek et al. (13) and GSE193068 from Seremet, Domizio et al. (14, 15) (Figure 3). Our human dataset is presented in Yildiz-Altay et al. (1), and is comprised of $n=6$ healthy and 12 biopsies from 10 DLE patients who were Black. *CXCR6* was upregulated in CLE skin vs. controls across all 3 species (Figure 3A–E). *CXCL16* was significantly elevated in Balb/c mouse, dog and Scholtissek et al. datasets, but did not reach significance for B6 mouse or skin of color patient samples (Figures 3F–J). To evaluate the possible utility of CXCR6 as a biomarker of cutaneous lupus, we performed Receiver Operator Characteristic curve (ROC)

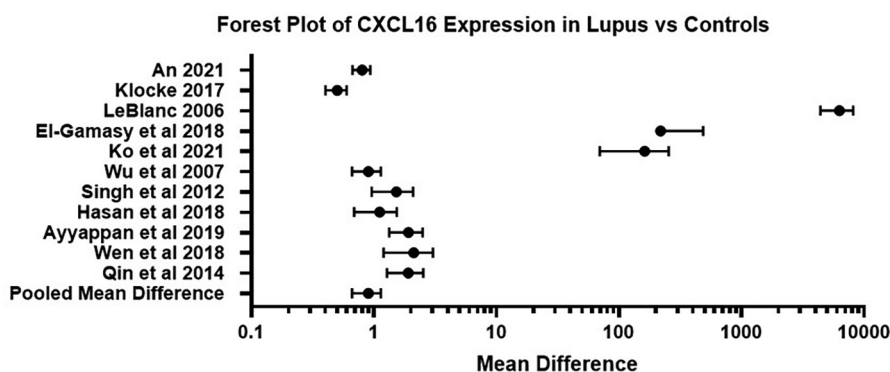


FIGURE 2

Forest plot of CXCL16 expression in lupus related conditions vs. control samples across studies. This forest plot summarizes the mean difference in CXCL16 levels between lupus affected individuals and healthy controls across 11 independent studies. Error bars represent 95% confidence intervals. A positive mean difference demonstrates higher CXCL16 expression in the lupus group of the study.

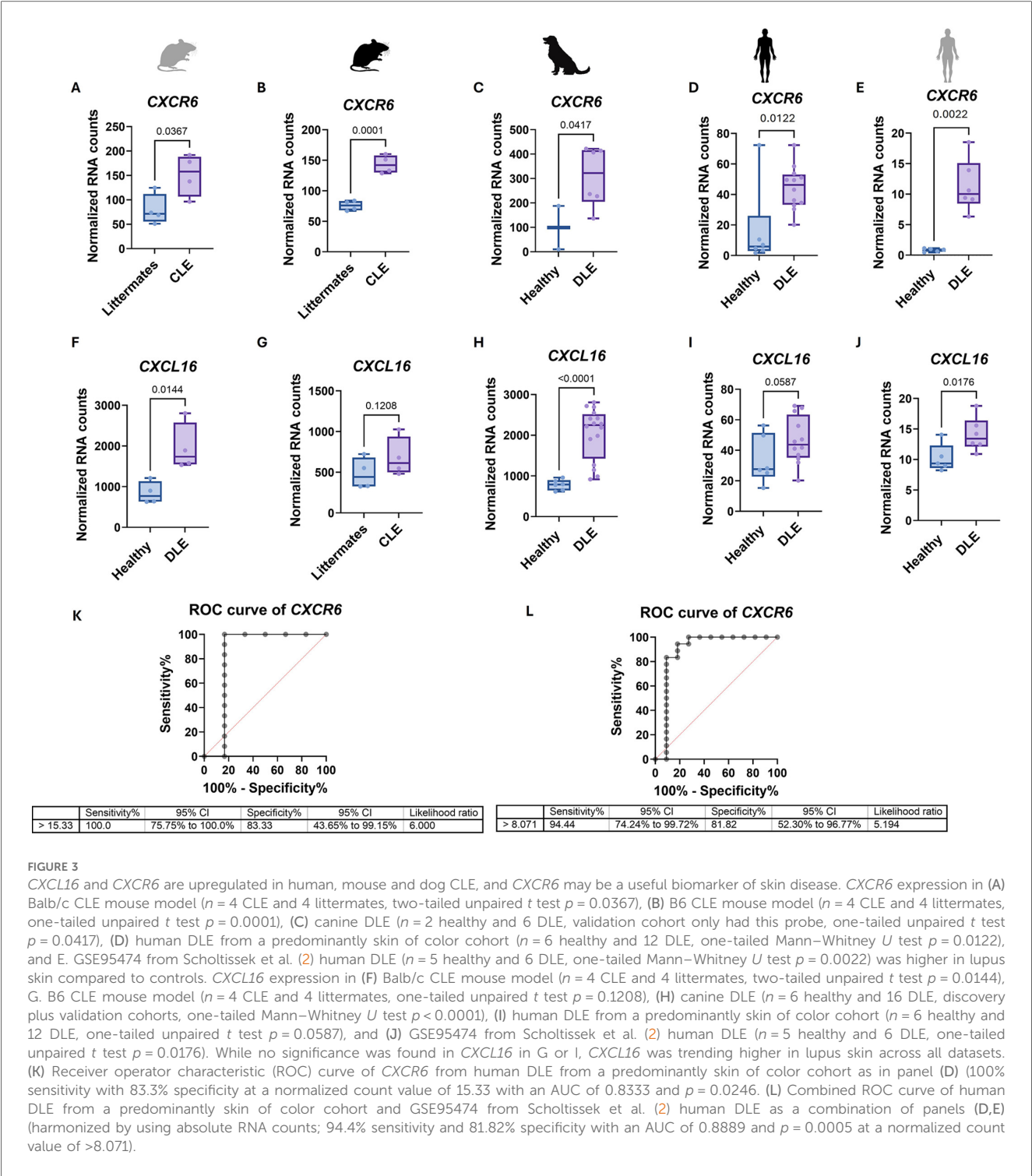


FIGURE 3
CXCL16 and *CXCR6* are upregulated in human, mouse and dog CLE, and *CXCR6* may be a useful biomarker of skin disease. *CXCR6* expression in (A) Balb/c CLE mouse model ($n = 4$ CLE and 4 littermates, two-tailed unpaired t test $p = 0.0367$), (B) B6 CLE mouse model ($n = 4$ CLE and 4 littermates, one-tailed unpaired t test $p = 0.0001$), (C) canine DLE ($n = 2$ healthy and 6 DLE, validation cohort only had this probe, one-tailed unpaired t test $p = 0.0417$), (D) human DLE from a predominantly skin of color cohort ($n = 6$ healthy and 12 DLE, one-tailed Mann–Whitney U test $p = 0.0122$), and E. GSE95474 from Scholtissek et al. (2) human DLE ($n = 5$ healthy and 6 DLE, one-tailed Mann–Whitney U test $p = 0.0022$) was higher in lupus skin compared to controls. *CXCL16* expression in (F) Balb/c CLE mouse model ($n = 4$ CLE and 4 littermates, two-tailed unpaired t test $p = 0.0144$), G. B6 CLE mouse model ($n = 4$ CLE and 4 littermates, one-tailed unpaired t test $p = 0.1208$), (H) canine DLE ($n = 6$ healthy and 16 DLE, discovery plus validation cohorts, one-tailed Mann–Whitney U test $p < 0.0001$), (I) human DLE from a predominantly skin of color cohort ($n = 6$ healthy and 12 DLE, one-tailed unpaired t test $p = 0.0587$), and (J) GSE95474 from Scholtissek et al. (2) human DLE ($n = 5$ healthy and 6 DLE, one-tailed unpaired t test $p = 0.0176$). While no significance was found in *CXCL16* in G or I, *CXCL16* was trending higher in lupus skin across all datasets. (K) Receiver operator characteristic (ROC) curve of *CXCR6* from human DLE from a predominantly skin of color cohort as in panel (D) (100% sensitivity with 83.3% specificity at a normalized count value of 15.33 with an AUC of 0.8333 and $p = 0.0246$). (L) Combined ROC curve of human DLE from a predominantly skin of color cohort and GSE95474 from Scholtissek et al. (2) human DLE as a combination of panels (D,E) (harmonized by using absolute RNA counts; 94.4% sensitivity and 81.82% specificity with an AUC of 0.8889 and $p = 0.0005$ at a normalized count value of >8.071).

analysis of *CXCR6* expression on our dataset, which revealed 100% sensitivity with 83.3% specificity at a normalized count value of 15.33 with an AUC of 0.8333 and P value 0.0246 (Figure 3K). Combining our dataset with Scholtissek et al, which we harmonized by using absolute RNA counts, generated an ROC with 94.4% sensitivity and 81.82% specificity with an AUC of 0.8889 and P value 0.0005 at a normalized count value of >8.071 (Figure 3L).

Discussion

CXCL16 is supported to be a biomarker of lupus nephritis and disease activity in both urine and serum samples in multiple studies from patient cohorts across the globe. Reyes-Thomas et al. also provided a nice meta analysis of the utility of *CXCL16* as a protein biomarker of lupus nephritis (28).

CXCR6 but not CXCL16 appears to be enriched in lupus skin, based on our dataset, Scholtissek et al. (13) and Ko et al. (27). We hypothesize this may be due to sun avoidance behaviors by patients, as CXCL16 expression is induced by UV light (3, 4). Work from Mempel lab (11) and Huang lab (12) recently demonstrated that Trm/Tem express CXCR6 in the context of melanoma. Thus, it is possible that the enrichment of CXCR6 in CLE skin could be due to the presence of memory T cells.

The CXCR6/CXCL16 axis is likely to contribute to tissue-specific inflammation in lupus through the recruitment of CXCR6+ effector T cells to the skin and kidneys. CXCL16 binding activates downstream signaling cascades including PI3 K/AKT, MAPK/ERK and NF- κ B, which promote immune cell survival, migration and cytokine release [reviewed in (29)]. Further studies should explore the therapeutic potential of targeting this axis, particularly its role in chronic tissue damage and T cell retention.

Limitations of our study include producing an exhaustive list of studies in our search strategy, such that we may have missed preclinical murine studies that identified CXCR6/CXCL16 in single cell RNA sequencing (30), or studies that may have captured CXCR6/CXCL16 in array technology without calling out individual measurements. Additionally, several studies were missing patient demographic data, and not all studies examined the impact of disease duration and/or treatment status on CXCR6/CXCL16 expression, which could contribute to bias in the interpretation of efficacy and reported results. Moreover, harmonization of measurement values would be important for establishing CXCR6/CXCL16 as a diagnostic or prognostic laboratory value for lupus disease and activity. These could include ELISA measurements of urine and serum CXCL16 protein levels, and skin CXCR6 RNA levels. Monitoring CXCR6 levels over time could also provide insight into its role and association with different pathological manifestations of CLE, including flare and non-flare conditions. This would provide knowledge of CXCR6 expression patterns that can lead to understanding disease activity and progression. Finally, for this study we excluded papers that were not in English. This may result in reduced generalizability, and possible incomplete evidence.

In conclusion, our systematic review and dataset meta-analysis supports CXCR6 and its ligand CXCL16 as biomarkers for lupus organ disease, specifically in the skin and kidneys. Our systematic analysis of primary studies demonstrates consistent upregulation of CXCL16 in serum, urine and cerebrospinal fluid in active lupus, while CXCR6 is enriched in lupus skin. These findings support a model in which the CXCR6/CXCL16 pathway contributes to tissue-specific inflammation and could serve as both a diagnostic marker and therapeutic target. Future studies should further elucidate the functional roles and therapeutic modulation of this axis across different lupus phenotypes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the UMass Chan IRB and the Howard University IRB with a Memorandum of Understanding (MOU) for cross-institutional studies. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants in accordance with the national legislation and institutional requirements. The dog animal studies were approved by the Cummings School of Veterinary Medicine at Tufts University IACUC. Written informed consent was obtained from the owners for participation of their animals in the biorepository. The studies were conducted in accordance with the local legislation and institutional requirements. The mouse animal studies were approved by the UMass Chan IACUC. The studies were conducted in accordance with the local legislation and institutional requirements. All datasets (human, dog, mouse) used in this study were acquired in previous studies and were re-queried for expression of CXCR6/CXCL16.

Author contributions

FK: Investigation, Data curation, Writing – review & editing, Visualization, Writing – original draft, Validation, Funding acquisition, Formal analysis, Project administration. HD: Validation, Investigation, Writing – review & editing, Formal analysis. VR: Investigation, Writing – review & editing, Data curation, Resources, Methodology. CF: Writing – review & editing, Investigation, Supervision, Resources, Project administration, Data curation. JR: Data curation, Supervision, Investigation, Writing – review & editing, Writing – original draft, Conceptualization, Visualization, Funding acquisition, Resources, Project administration.

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Conflict of interest

JR is an inventor on use patents for human and veterinary CTCL diagnostics, and targeting CXCR3 and IL15 for the treatment of vitiligo.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/flupu.2025.1645416/full#supplementary-material>

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