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Current Insights in Cutaneous Lupus Erythematosus Immunopathogenesis

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Cutaneous Lupus Erythematosus (CLE) is a clinically diverse group of autoimmune skin diseases with shared histological features of interface dermatitis and autoantibodies deposited at the dermal–epidermal junction. Various genetic and environmental triggers of CLE promote infiltration of T cells, B cells, neutrophils, antigen presenting cells, and NK cells into lesional skin. In this mini-review, we will discuss the clinical features of CLE, insights into CLE immunopathogenesis, and novel treatment approaches.

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INTRODUCTION

Cutaneous Lupus Erythematosus (CLE) is an autoimmune disease primarily affecting skin and mucosal tissue. Total CLE disease incidence is ∼4.3 per 100,000 (1, 2). CLE exhibits a strong sex bias toward females much like systemic lupus erythematosus (SLE) (3–5). Certain CLE subtypes may progress to SLE (6, 7), which can have health consequences, including kidney and brain involvement leading to renal failure and neurologic disease (8). Successful treatment of cutaneous disease may significantly decrease the risk of systemic involvement (9). Treatment options for CLE are limited, with anti-malarials as the most commonly prescribed drugs, followed by calcineurin inhibitors, mycophenolate mofetil, methotrexate, and steroids (10–13).

CLINICAL FEATURES OF CLE

CLE encompasses a heterogeneous group of photodermatoses with varying degrees of association with systemic disease (SLE) [reviewed in (14)]. It is typically classified into three main subtypes based on the disease chronicity, clinical morphology and distribution: acute (ACLE), subacute (SCLE), and chronic (CCLE) (15, 16). All CLE subtypes are characterized histopathologically by interface dermatitis (with the exception of tumid lupus and lupus panniculitis) and lupus band reaction, which consist of infiltration of immune cells and deposition of autoantibodies at the dermal-epidermal junction (DEJ) (17).

ACLE presents as transient erythematous patches that correspond to flares in SLE patients. A well-known example of ACLE is the malar rash, or butterfly rash, that classically crosses both cheeks but spares the nasolabial folds. This helps to distinguish it from other clinical mimickers such as rosacea and seborrheic dermatitis. ACLE can affect the entire body in some patients with bad flares, and is considered a criterion for the diagnosis of SLE. Up to 80% of SLE patients experience malar rash, which typically flares with UV exposure but does not leave any scar or dyspigmentation. Histologically, ACLE manifests as lymphoplasmacytic interface dermatitis with vacuolar changes at the DEJ associated with mucin deposition.

Lesions of SCLE last longer than the malar rash of ACLE, but systemic lupus occurs in a significantly lower percentage of the affected individuals. SCLE most often occurs on the photo-exposed areas of the upper chest, back, and external upper extremities (**Figure 1**). When active, it typically presents as papulosquamous lesions and/or annular plaques (psorasiform) with central clearing and raised erythematous scaly edges. Upon resolution, SCLE can leave dyspigmentation but no permanent scarring. SCLE is highly associated with anti-Ro/SSA autoantibodies. In patients with new-onset SCLE, it is important to carefully review medications, as SCLE can be induced by nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, antihypertensives, and antifungals (18).

CCLE has multiple subtypes, and the most common is discoid LE (DLE). DLE commonly presents as red, atrophic, and hypopigmented plaques with a characteristic rim of hyperpigmentation. DLE typically only affects areas above the neck such as scalp, ears, nose, and cheeks (localized DLE). Presence of DLE is one of the diagnostic criteria of SLE and is observed in 20% of the patients with systemic disease; however, only 5–10% of cases with isolated DLE eventually progress to develop systemic disease (4). When it occurs on the scalp, DLE can cause irreversible scarring alopecia (19). Though rare, DLE may affect larger areas of the body including trunk and upper extremities (generalized DLE), which confers an increased risk of systemic involvement. DLE exhibits more prominent histopathological findings including follicular plugging, periadnexal lymphoplasmacytic infiltrate, and pigment incontinence. Other variants of CCLE, including tumid lupus, chilblain lupus, and lupus panniculitis, are significantly less frequent.

AUTOANTIBODIES/AUTOANTIGENS

Like SLE, many CLE patients develop autoantibodies including anti-nuclear antibodies (ANAs). Antibodies against Ro/SSA and La/SSB are detected frequently and have been associated with SCLE and neonatal lupus erythematosus (NLE), in addition to SLE and Sjogren's Syndrome (20–24). Most CLE patients exhibit anti-Ro/SSA autoantibody reactivity patterns (25). Ro refers to ribonucleoproteins that are encoded by two separate gene products, resulting in 52 kDa (also known as TRIM21) and 60 kDa (also known as TROVE2) protein isotypes (26). CLE patients react more frequently to the 60 kDa form than the 52 kDa form (27). Anti-Ro autoantibodies may also be mechanistically involved in CLE pathogenesis, as commensal bacteria that produce a Ro60 kDa ortholog can trigger lupus development in mice (28). Infusion of anti-Ro/SSA into human skin grafted mice results in lupus band reaction similar to what is observed in CLE specimens (29).

Other autoantigens in CLE include SSB/La, ribonucleoprotein, smith (sm) antigen (30), C1q (31), and HMGB1 (32). UV damage can induce translocation of these autoantigens to the surface of keratinocytes, thereby making them bioavailable to the immune system (33–36). HMGB1 appears to play a significant role in the development of CLE: HMGB1 is highly expressed in the epidermis of CLE skin biopsies (37) and expression level correlates with clinically active photoinduced CLE lesions (38, 39).

A recent study in a cohort of Italian CLE patients found strong correlations between autoantibody specificities and CLE subtypes (40). CCLE is negatively associated with anti-extractable nuclear antigens (ENA), anti-Ro/SSA, and anti-dsDNA. SCLE positively correlates with ENA, anti-Ro/SSA, anti-Smith, and anti-RNP. ACLE is strongly associated with anti-dsDNA and ANA, though this may be due to the finding that these autoantibodies are found in higher frequencies in females and SLE patients.

NLE is a condition characterized by cutaneous, cardiac, and multi-systemic abnormalities observed in 5–16% of newborn infants whose mothers have autoantibodies against Ro/SSA, La/SSB, and U1-ribonucleoprotein (41–44), regardless of whether the mothers are symptomatic or not (45). Autoantibodies against Ro/SSA and La/SSB were detected in 98% of affected infants (45). Anti-Ro52/60-kDA Ro/SSA and 48-kD La/SSB auto-antibodies contribute to heart block (46), whereas 50-kD La/SSB are associated with cutaneous disease (47, 48), which is thought to self-resolve but can have long-term cutaneous changes (49). A study of 186 antibody exposed fetuses and infants indicates a direct correlation between the amount of maternal anti-Ro and anti-La antibodies and fetal tissue injury (48).

CLE IMMUNOPATHOGENESIS

Factors Contributing to Onset

Like many complex diseases, CLE is thought to arise from a combination of genetics and environment. Several immune genes have been implicated in subtypes of CLE, including cytokine genes, complement genes, and innate immune genes [reviewed in (50)]. Polymorphisms in the transcription factor IRF5, the signaling molecule TYK2, and the immune regulator CTLA4 were identified in a Finnish cohort of CLE patients (51). Familial chilblain lupus, a rare form of CLE characterized by acral lesions, is caused by gain-of-function mutations in the DNA sensor protein STING (52, 53), or mutations that decrease the exonuclease activity of TREX1 (54–56).

CLE and cutaneous involvement in SLE can be induced by UV radiation, and photosensitivity is a criterion used by the American College of Rheumatology for lupus diagnosis [reviewed in (57, 58)]. The pathogenic wavelengths of UV radiation remain unclear. However, UVB is considered an instigating factor, as the dosage required to induce erythema is 1,000 fold less than that of UVA in lupus patients (59). Lupus keratinocytes are more sensitive to UV light than healthy keratinocytes (60), and exhibit aberrant apoptosis thereby generating cellular debris and activating the immune system (57). Some groups have reported impaired clearance and accumulation of apoptotic keratinocyte debris in afflicted skin (61), while others have found inflammatory clearance with no evidence of impaired clearance (62). Regardless of clearance efficacy, it is clear that UV damaged, apoptotic keratinocytes are one of the main instigating factors in CLE lesion formation. A recent review by Wolf et al. (63) summarized known aspects of UV-induced CLE.

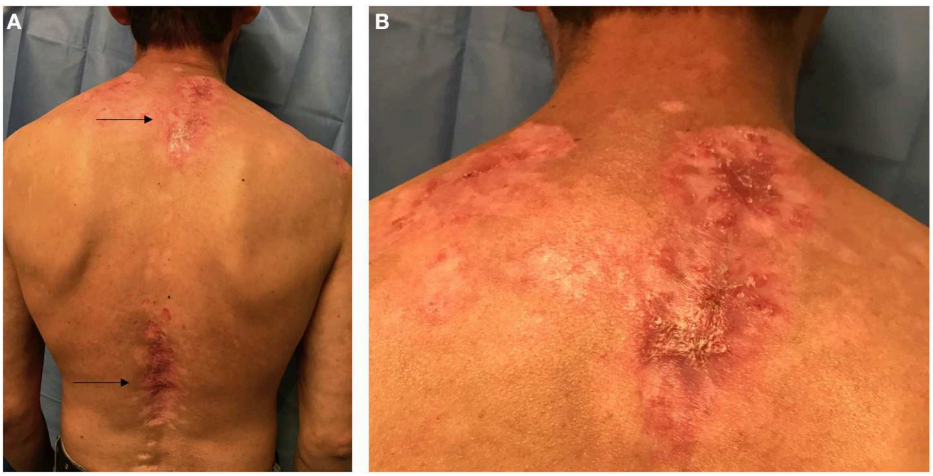

FIGURE 1 | Posterior view of the trunk in a Hispanic patient with Cutaneous Lupus Erythematosus (CLE). **(A)** Arrows point to two lupus patches on the upper back and lower back. **(B)** Closer view of the upper back patch in the intrascapular area showing scaling, erythema, dyspigmentation, and scarring.

Over 100 drugs have been identified that induce CLE or CLE flares (18, 64–66), with SCLE being the most common clinical subtype induced by prescribed medications such as antihypertensives and antifungals (67). The blood pressure medication hydrochlorothorazide induces SCLE in a photosensitive manner (68). The chemotherapeutic 5-fluorouracil can cause SCLE or DLE (69, 70). Proton pump inhibitors such as omeprazole are triggers of SCLE (71, 72). There are a few case reports of CLE resulting after anti-TNF therapy, though the etiology is not fully understood (73).

Smoking is a trigger of CLE (74), particularly DLE (75), and reduces responsiveness to anti-malarial treatments (76, 77). Counseling patients to quit smoking can significantly improve CLE and other autoimmune conditions (77–80). Case reports demonstrate environmental or occupational exposures can also induce CLE, such as silica exposure (81, 82). Lastly, microbes may trigger CLE: recent studies found *Staphylococcus aureus* can colonize skin following IFN-mediated barrier disruption (83), and is enriched in CLE lesional skin (83).

Sensing Damage: Innate Immune Cells

UVB radiation and/or drugs cause keratinocyte damage and death, which is sensed by the innate immune system to create a feed-forward loop driving pathogenesis. Keratinocytes themselves can respond to TLR-independent nucleic acid ligands via MDA5, RIG-I, c-GAS and STING, and can activate the AIM2 inflammasome, which can initiate the interferon response [reviewed in (84)]. Thus, they can respond to bystander damage to alert the immune system.

Langerhans cells are specialized dendritic cell (DC) populations that live in the epidermis, and migrate to skin draining lymph nodes upon antigen encounter (85). UVB-induced keratinocyte damage is sensed by Langerhans cells in both lupus-prone [MRL/lpr and B6.SLE1yaa (86)] and wild type mice (87). Shipman et al. (86) demonstrated that ADAM17 is upregulated in Langerhans cells following UVB exposure, which in turn increases conversion of EGFR ligands into an active form in an attempt to protect keratinocytes from further UVB damage. In murine SLE models, Langerhans cells have a reduced ability to process EGFR ligands into an active form, resulting in a dysfunctional LC-KC axis in CLE lesions. LCs are subsequently replaced by other inflammatory DC subsets, thereby promoting further inflammation (88, 89) (**Figure 2A**). These data are supported by a recent microarray study of CLE biopsies that demonstrated decreased EGFR signaling pathways (90).

One particularly important inflammatory DC subset contributing to CLE pathogenesis is plasmacytoid DCs (pDCs). pDCs are common in DLE, and are used by dermatopathologists to assist in diagnosis (91). When presented with DNA, pDCs potently upregulate Type-1 IFN, mainly IFNα. pDCs are a key source of Type-1 IFN in lupus lesional skin (92, 93), and UVB promotes their recruitment to the skin (94). A first-in-human study of BDCA2 antibody (BIIB059), which targets pDCs, for SLE decreased expression of IFN response genes in blood, normalized MxA expression, reduced immune infiltrates in skin lesions, and decreased CLASI-A score [(95), NCT02847598]. BIIB059 is now in a phase-2 clinical trial for SLE and active CLE treatment (NCT02847598).

In addition to apoptotic keratinocytes, another potential source of DNA that could activate pDCs in the skin is from neutrophils. Some neutrophils have the ability to produce neutrophil extracellular traps (NETs), which are comprised of DNA, chromatin and various proteins. NETs have been found in various CLE subtypes including: lupus panniculitis, ACLE, DLE, and to a lesser extent, SCLE (96). Though the study by Safi et al. (96) included a cohort of only 30 patients, their work indicates the presence and contribution of NETs in CLE is worth further investigation. A subclass of neutrophils, called low density granulocytes (LDGs), have an increased propensity for producing NETs. LDGs have been reported in the skin of SLE patients (97). LDGs NETs provide a source of autoantigens, and may interact with nucleic acids from UV-B damaged KCs. Subsequent accumulation of apoptotic DNA provides a potential mechanism by which skin lesions are initiated or sustained (98) (**Figure 2B**).

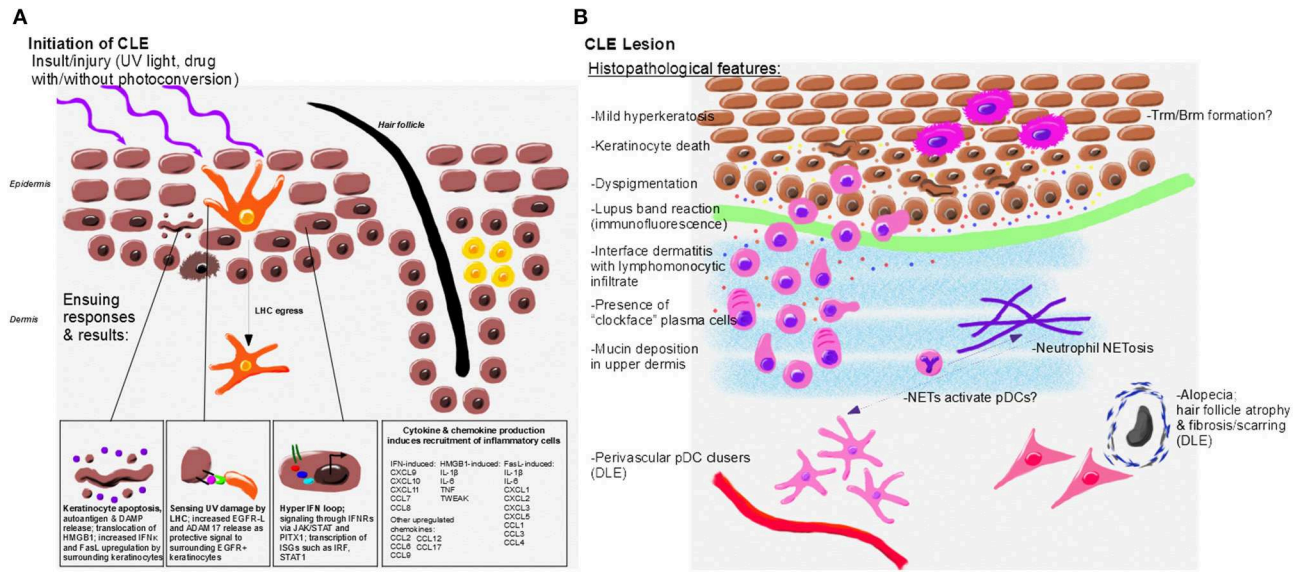

FIGURE 2 | Initiation, immunopathogenesis, and histopathologic features of CLE. **(A)** Environmental triggers of CLE include UV light and drugs which may become photoconverted to induce translocation of autoantigens, DAMP release and keratinocyte death. UV damage is sensed by LHC, which protect surrounding keratinocytes through release of EGFR-L; however, LHC are decreased or absent in CLE lesional skin. Keratinocytes from CLE patients also exhibit a hyper IFN loop via JAK/STAT signaling to release IFNs. Keratinocytes and skin resident immune cells upregulate cytokines and chemokines in response to IFN and other signals to promote lesion formation. **(B)** Histopathological features of CLE lesions include mild hyperkeratosis, keratinocyte death and debris, lymphocytic infiltrates, interface dermatitis, and mucin deposition. Dyspigmentation occurs in some CLE subtypes. Perivascular pDC clusters and fibrosing alopecia occur primarily in DLE lesions. CLE interface dermatitis is comprised of lymphomonocytic infiltrates with "clockface" plasma cells. Neutrophils, which may form NETs, are also present in CLE lesions and may activate pDCs through release of DNA and other autoantigens. Resident memory T and B cells likely form in CLE lesions. Inflammatory mediators drive continued recruitment and damage in the lesion, including IFNκ (yellow, associated with keratinocytes), IFNγ (orange, associated with the infiltrating immune cells), CXCL9 (red, amplified by keratinocytes and immune cells), and CXCL10 (blue, amplified by keratinocytes and immune cells).

Like DC populations, macrophages and monocytes are also involved in debris clearance and sensing of DAMPs. Immunohistochemical studies demonstrated that $CD68^+$ macrophages express FasL and are densely populated near hair follicles in CLE lesions (99). Inflammasome activity in blood monocytes from SLE patients is enhanced via type I IFN-mediated upregulation of IRF1 (100), though the functional capacity of macrophages in CLE has not been well-studied. A trial of macrophage colony-stimulating factor (MCSF) antibody failed to reduce immune infiltrates or activation in CLE lesions and did not improve CLASI score (101). Thus, it is possible that tissue macrophages in CLE lesions perform an immune regulatory function, require different cytokines for their function/survival, or are dispensable for CLE.

Another aspect of innate immune involvement in lupus is the uptake and processing of cellular debris for both clearance and presentation of autoantigens. The scavenger receptor C1q binds to keratinocyte apoptotic blebs to assist their clearance (102). A silent single nucleotide polymorphism (SNP) in C1QA gene ($Gly70_{GGG/GGA}$) results in lower serum C1q and is associated with SCLE (103).

Promoting Damage: Lymphocytic Infiltrates

Inflammatory infiltrates in CLE are comprised mainly of T lymphocytes, with other infiltrating cells including B cells/plasma cells, NK cells, dendritic cells (104, 105), and in some subtypes, neutrophils (106), implicating these populations as key drivers of inflammation in CLE lesions. The T cell specificities in CLE skin are unknown, but SLE studies identified T cells reactive to nucleosomes/histones (107), which can induce anti-dsDNA antibody production (108). TCR-Vβ38 and Vβ13 were enriched in skin of CCLE patients, implicating oligoclonal expansion (109). Several studies have observed expression of cytotoxic markers characteristic of T cell function, such as Th1-related cytokines and granzyme B (110, 111). Interestingly, the perforin promoter (112), CD70 promoter (113), and other loci (114) are hypomethylated in $CD4^+$ T cells from SCLE patients, making them poised to transcribe effector molecules. Both $CD4^+$ and $CD8^+$ circulating T cells have higher HLA-DR expression in CLE patients, and higher CD25 in DLE patients specifically, compared to healthy controls (115). Tregs are lower (116, 117), and γδ T cells are higher (118), in CLE lesions. Skin-infiltrating $CD4^+$ T cells express FasL have the potential to ligate Fas and can induce apoptosis in keratinocytes and other infiltrating immune cells (99).

Plasma cells in lupus skin lesions are often observed as "clockface" cells (119). It is not clear whether lupus band reactions arise from local production of autoantibodies in the skin by plasma cells, or if they deposit in the skin from the circulation. Interestingly, while B cells are required for development of lupus in mice (120, 121), autoantibody formation

appears to be a byproduct of lupus immune responses and not a driving factor: MRL-lpr mice with B cells incapable of secreting immunoglobulin develop nephritis, implicating B cells' antigen presenting function as being critical for lupus development (122). It is unclear which B cell functions are required for CLE, though preclinical studies using chimeric antigen receptor T cells (CAR-Ts) directed against B cells ameliorated skin disease in lupus-prone mice (123). Furthermore, B cell depletion with rituximab showed efficacy in a case study of 4 lupus panniculitis patients with childhood onset who were refractory to other standard treatments (124), and ameliorated skin symptoms in a retrospective case study of 14 consecutive SLE, one CCLE and two SCLE patients with recalcitrant skin involvement (125).

The atypical lymphocyte marker CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) is highly expressed in CLE lesional skin. CD38 was recently shown to be important for Tfh-B cell collaboration in response to recurrent influenza vaccination (126). Polymorphisms in intron 1 of CD38 are associated with the development of DLE in a Spanish patient population (127). It is unclear what role CD38 plays in CLE pathogenesis, though knocking CD38 out of MRL-lpr mice accelerates lupus (128).

NK cells have been studied in peripheral blood from SLE patients, though their precise roles in CLE and skin are not known due to a paucity of mechanistic studies. In the SLE studies, blood NK numbers decrease with increased lupus disease activity and/or exhibit defects in traditional killing functions (129–131); though rare populations are often expanded and secrete higher levels of IFNγ compared to healthy controls (132–135). Given their roles in sensing cellular stress (136), clearing tumors (137, 138), and keratinocyte-derived tumors in particular (139), it is likely that NK cells are also able to kill stressed keratinocytes following UV or drug injury to promote CLE lesions. It is also possible that T cells expressing killer receptors contribute to keratinocyte death in CLE, as exemplified by NKG2D ligation on mouse dendritic epidermal T cells (DETCs): in the absence of TCR signaling, NKG2D ligation on DETCs induces IFNγ production and causes keratinocyte cytotoxicity (140). In line with this, one study found invariant NK T cells (iNKTs) were enriched in SCLE and DLE patient blood by flow cytometry and in lesional skin by immunohistochemistry (141): they expressed IFNγ *in situ*, and were Ki67+, indicating they were proliferating in skin lesions.

Chemokine Recruitment of Leukocytes to CLE Lesions

Type 1 IFN and type 2 IFN signaling stimulates expression of CXCL9, CXCL10, and CXCL11 which mediate leukocyte migration to peripheral tissue via CXCR3. IFN and CXCR3 have been postulated to drive the pathogenesis of all subtypes CLE (142), mediating the recruitment of the aforementioned immune cell types and providing positive feedback loops for T cell and pDC recruitment. Previous studies reported CXCR3 ligand expression in the skin in all the different subtypes of CLE (57, 58, 104, 143). Further, UV light induces upregulation of CXCR3 ligands in keratinocytes, linking the environmental insult to the recruitment of pathogenic immune cells (58).

Type 1 IFN also induces CXCL13 (144), which can support germinal center formation through migration of Tfh cells and B cells [reviewed in (145)]. While CXCL13 serves as a biomarker of SLE but not CLE (146), epidermal injury can accelerate nephritis in NZM2328 mice via upregulation of CXCL13 (147). The receptor for CXCL13, CXCR5, can influence B cell function by enhancing antigen uptake via membrane ruffling and LFA-1-mediated adhesion, and integrating BCR signaling in motile cells (148). The precise role of CXCL13 in CLE is not known.

CCL17 is expressed by keratinocytes in CLE lesions and has been hypothesized to recruit $CD8^+$ T cells bearing the cognate receptor CCR4 to the skin in scarring CLE (149). iNKT cells in CLE lesions also express CCR4, and blood iNKTs express higher levels of CCR4 and CCR6 than healthy controls (141). Higher CCR5 and lower CCR3 expression on peripheral CD4+ T cells is associated with higher disease activity in CLE (150).

Gene expression analysis of human DLE and SCLE skin biopsies, as well as a mouse model of CLE, exhibited increased CCL3, CCL4, CCL7, and CCL8 (151). While the precise roles of these chemokines in CLE have yet to be elucidated, inferences can be made based on their previously established biological activities. Future studies will need to be conducted to determine how these chemokines guide specific immune populations to and through the skin during CLE.

Paracrine Signals: Cytokines, Hormones, and Master Regulators

The inflammatory signatures of CLE are interferon (IFN)-based: a recent microarray study of 90 CLE biopsies found increased IFN pathways in all CLE subtypes, and DLE samples had a unique IFNγ node (90). Interestingly, the authors found no differences between skin biopsies of patients with and without systemic involvement. Blocking IFNα receptor improved CLASI scores for SLE patients with cutaneous involvement in a phase II trial [(152, 153), reviewed in (154)]; however IFNγ blockade did not improve CLASI scores in DLE patients (155). Single cell resolution may be necessary to elucidate the precise roles of different IFNs in pathogenesis.

Keratinocytes from CLE patients exhibit an enhanced response to both type-1 and type-2 IFNs (156), and produce IFNκ (157), IL-6 (158), and Type-III IFN (IFNλ) following UVB damage. Cytokine dysregulation in UVB treated CLE keratinocytes provides a link between UV initiation factors and immunopathogenesis (156). UV treatment of keratinocytes induces upregulation of IFNκ, which plays a key homeostatic role in maintaining IFN balance in skin (158). Lupus keratinocytes derived from active CLE lesions and nonlesional skin constitutively overexpress IFNκ, which increases photosensitivity via plasmacytoid DC production of IFNα in response to IFNκ signaling (157).

Higher levels of Th1 and Th17 cells in CLE lesions have been reported, along with IL-21 (159). IL-21 activates pDCs to produce granzyme B (160), thereby enhancing keratinocyte killing by NK cells. Interestingly, Salvi et al. (159) found that type I IFN served as a negative regulatory loop for granzyme B production by pDCs. This implies that high levels of type I IFN

in skin are not pathogenic, but rather represent an attempt to counter inflammation.

The contribution of female sex hormones in CLE remains unclear. One epidemiological study noted premenstrual and perimenopausal flares (161), indicating that a certain level of estrogen is protective. Nevertheless, the addition of estrogen to keratinocyte cultures doubles Ro/SSA surface expression following UVB exposure (162) and enhances binding of anti-Ro/SSA and La/SSB autoantibodies to the plasma membrane (163). A patient who received estrogen as part of sex reassignment surgery developed tumid lupus following UV exposure (164). Estrogen can positively regulate the IFNγ promoter (165) and NK cell activity (166), possibly explaining other roles in CLE pathogenesis.

Vgll3 is a transcription co-factor that governs expression of inflammatory genes associated with autoimmunity, including CLE (167). Vgll3 is more highly expressed in female skin and in lupus patient skin regardless of gender. Overexpression of Vgll3 in male mice makes skin appear more "female-like" and promotes both skin and systemic autoimmune attack (168).

CONCLUSION

The complexity of CLE has made it difficult to fully elucidate pathogenesis, with genetic and environmental triggers causing both innate and adaptive immune activation that creates diverse clinical manifestations. Nevertheless, increased knowledge in this field has paved the wave for promising new drugs in CLE. Blocking IFNAR antibody (Anifrolumab) improved CLASI scores in a phase IIb double-blind trial (>50% improvement, $p = 0.013$) (152, 153). Rituximab B cell depletion showed efficacy in case reports of CLE subtypes and SLE with skin involvement (124). The JAK/STAT pathways mediate signaling for a myriad of cytokines, including IFN, and other biological processes. JAK inhibition with tofacitinib (JAK3>JAK1>JAK2), baricitinib (JAK1/2) or ruxolitinib (JAK1/2) showed efficacy for familial chilblain lupus in human case studies and small clinical trials (53, 169–171). However, filgotinib (JAK1) did not reach its primary endpoint in a phase II double blind study, underscoring the need for a better understanding of which JAKs and STATs drive CLE (172–174). Similarly, the roles of IL-12 and IL-23 need to be revisited, as ustekinumab has been reported to both treat (175–178) and cause CLE (179).

Another approach to treat CLE is to enhance Treg function. The immune-dampening peptide Edratide, which stimulates Tregs, was safe in a phase II trial for SLE and improved BILAG score, but did not meet its primary endpoint (180). CAR-Tregs, which have been shown to be efficacious in a mouse model of asthma (181), may provide another approach, though they have yet to be tested for lupus (182). Of note, a challenge that remains in all CLE and lupus trials is the fact that patients are maintained on immunosuppressive drugs to keep their autoimmunity in check, which may have the unintended consequence of masking true efficacy. Ultimately, novel immunotherapies will need to be tested and developed for treatment of all CLE subtypes.

ETHICS STATEMENT

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MAR: patient photos and consent and figure generation. JR: artwork/figure generation. MR: clinical section. ZR-O: innate immune genes/receptors of cellular debris section. PN: autoantibodies/autoantigens section. CG and JR: all other sections. All authors approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: JR is an inventor on patent application #62489191, "Diagnosis and Treatment of Vitiligo" which covers targeting IL-15 and Trm for the treatment of vitiligo; and on patent application #15/851,651, "Anti-human CXCR3 antibodies for the Treatment of Vitiligo" which covers targeting CXCR3 for the treatment of vitiligo. JR is a reviewer for Frontiers Immunology journal.

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.