The Genetic Landscape of Cutaneous Lupus Erythematosus

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Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disease that can exist as a disease entity or within the context of systemic lupus erythematosus (SLE). Over the years, efforts to elucidate the genetic underpinnings of CLE and SLE have yielded a wealth of information. This review examines prior studies investigating the genetics of CLE at the DNA and RNA level and identifies future research areas. In this literature review, we examined the English language literature captured within the MEDLINE and Embase databases using pre-defined search terms. First, we surveyed studies investigating various DNA studies of CLE. We identified three predominant areas of focus in HLA profiling, complement deficiencies, and genetic polymorphisms. An increased frequency of HLA-B8 has been strongly linked to CLE. In addition, multiple genes responsible for mediating innate immune response, cell growth, apoptosis, and interferon response confer a higher risk of developing CLE, specifically TREX1 and SAMHD1. There was a strong association between C2 complement deficiency and CLE.

Second, we reviewed literature studying aberrations in the transcriptomes of patients with CLE. We reviewed genetic aberrations initiated by environmental insults, and we examined the interplay of dysregulated inflammatory, apoptotic, and fibrotic pathways in the context of the pathomechanism of CLE. These current learnings will serve as the foundation for further advances in integrating personalized medicine into the care of patients with CLE.

Keywords: cutaneous lupus erythematosus, DNA, RNA, genetic polymorphism, microarray, inflammation, apoptosis, fibrosis

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a heterogeneous autoimmune disease that can be skin-limited or exist within the context of systemic lupus erythematosus (SLE). With the advancement of genetic sequencing technology at the DNA and RNA level, more dysregulated pathways and gene networks that contribute to the development of CLE have been identified. Specifically, differential expression of key genes involved in various pathways, such as inflammation, apoptosis, and immunity has revealed a complex, heterogeneous picture. These new gene expression profiles offer

Abbreviations: BAFF, B-cell activating factor; CCLE, chronic cutaneous lupus erythematosus; circRNAs, circular RNAs; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LET, lupus erythematosus tumidus; lncRNAs, long non-coding RNAs; NLE, neonatal lupus erythematosus SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; SYK, spleen tyrosine kinase.
the opportunity to further delineate classification subsets of CLE and potentially predict prognosis, such as response to treatments and progression to systemic disease (1, 2).

Up until recently, the development of new therapies for CLE has been stymied by an incomplete understanding of the underlying pathophysiology of CLE. Given the importance of understanding the genetic landscape of CLE, we performed a literature review to summarize studies examining DNA and RNA genetic aberrations in CLE.

METHODS

This was a review of the English-language literature captured within the MEDLINE and Embase databases using pre-defined search terms (Supplementary Table 1) from inception through 7 February 2022. Two independent reviewers (H.W.C. and G.B.) reviewed all studies, and a third reviewer (B.F.C.) resolved any discrepancies. Inclusion criteria were original studies, case series, and case reports related to CLE in humans in the English language. Articles underwent title and abstract screening with a subsequent full-text review. Articles were included if their findings were pertinent to DNA or RNA in the context of CLE. Reviews, conference abstracts, editorials, and all non-peer-reviewed findings were excluded from this review. In total, 1,253 studies were identified for screening, and 105 studies were ultimately included for final review after applying inclusion and exclusion criteria (Supplementary Figure 1).

RESULTS

DNA

Studies examining DNA have long been performed to better our understanding of cutaneous lupus. Three major themes emerged from our review of these studies, such as HLA profiling, complement deficiencies, and genetic polymorphisms.

Human Leukocyte Antigen Genes Have Been Associated With CLE and Its Subtypes

Human leukocyte antigen (HLA) is quintessential in the differentiation of self and non-self and plays a strong role in autoimmunity. HLA profiling studies have been performed in small groups of patients with CLE and controls to better understand genetic variations. Fowler et al. (3) found an increased frequency of HLA-DRw6 among both White and Black patients with CLE. In further studies, HLA-B8 has repeatedly been found to be increased among patients with discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) (4–7). Bielsa et al. (4) found an increased frequency of HLA-B8 and HLA-DR3 along with a decreased frequency of HLA-DR5 in patients with annular SCLE when compared with controls. Another study of 11 Finnish patients with SCLE and 23 controls showed that HLA-DR3, HLA-B8, and HLA-DR2 were higher in patients with SCLE vs. controls (7). Fischer et al. (8) found the HLA-DQA1*0102 allele was significantly increased among 26 patients with chronic CLE (CCLE) vs. healthy controls. The HLA-DQA1 alleles have also been studied in neonatal lupus erythematosus (NLE), with mothers of seven NLE children all carrying at least one DQA1 allele with glutamine at position 34 of the first domain compared with just 44% of controls (9). Another study of 28 patients with DLE showed a higher frequency of HLA-DRB1*04 (10). These studies highlight the inherent importance of HLA variations in CLE, though many are limited by small sample sizes. Larger studies, such as genome-wide association studies, in diverse populations, would help elucidate these variations.

Deficiencies in the Complement Cascade Contribute to Cutaneous Lupus Erythematosus Pathogenesis

The complement cascade is indispensable in mediating phagocytosis and inflammation. C1q is a subcomponent of C1 comprised of three heterotrimeric subunits (C1qA, C1qB, and C1qC). In a cohort of 19 White patients with SCLE, homozygous C1qA A > G transition mutation in exon 2, which results in a synonymous mutation, was found to occur more frequently in patients with SCLE relative with healthy controls (11). Despite no alterations in the protein sequence, decreased C1q protein was still observed. Another case study identified a homozygous G > C transversion mutation in C1qC exon 1, resulting in a Gly61Arg mutation (12). Multiple case studies have identified C2 deficiency in patients with SCLE and DLE (13–15). The gene encoding C2 lies within the major histocompatibility complex and is thus linked with HLA-A10, -A25, -B18, -DR2, and -Dw2. Agnello et al. (16) examined the pedigrees of four patients with DLE and found a partial genetic deficiency of C4 in patients carrying the null C4 allele B*QO. Given the important function of the complement cascade in mediating phagocytosis and inflammation, further studies on the complement system’s role in the pathogenesis of CLE would be beneficial.

Genetic Polymorphisms Have Been Featured in Familial Chilblain Lupus and Other Cutaneous Lupus Erythematosus Subtypes

Genetic polymorphisms have also been a frequent focus of study for lupus. Table 1 summarizes prominent ones that have been identified, such as TREX1, SAMHD1, and tumor necrosis factor (TNF). TREX1 has been identified as a significant factor in familial chilblain lupus. Günther et al. (17) identified a potential mutation hotspot for TREX1 where 4 of 6 families affected by familial chilblain lupus all present the same mutation. Günther et al. (18) also linked TREX1 with the upregulation of type I interferon (IFN) activity in familial chilblain lupus. Another case report of a family with familial chilblain lupus revealed that three affected individuals all carried the same heterozygous mutation (19). Heterozygous mutations in SAMHD1 have also been found in patients with familial chilblain lupus independently of TREX1 mutations, as reported by Ravenscroft et al. (20). Further, Lenggrosegoro et al. (21) found a deletion of the SAMHD1 gene’s initiator region in a child with familial chilblain lupus, who did not show an increased IFN signature. TNF is another gene investigated extensively in lupus. Mutations involving this gene seem to be distinctly associated with SCLE rather than DLE (6, 22, 23). Millard et al. (6) reported a
TABLE 1 | Genetic polymorphisms investigated in cutaneous lupus studies and their functions.

| Gene     | Function                                                                 | Relevance to CLE and its subtypes                                                                 |
|----------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| C1QA     | Encodes the C1q subcomponent of the C1complement system                  | SNP of gene has significant association with SCLE compared to normal (11)                        |
| CSNK2B   | Subunit of a protein kinase for regulation of metabolic pathways and DNA replication and transcription and mRNA translation | Has SNP strongly associated with CLE (26)                                                        |
| CTLA4    | Protein involved in signaling T cell inhibition                           | Higher disease risk for DLE from haplotype variation (29)                                        |
| HLA-DRB3 | Cell surface molecule for antigen presenting cells. Presents extracellular protein derivatives for immune response | Independent SNP with a high association with CLE (26)                                             |
| HLA-DQA1 | Cell surface molecule for antigen presenting cells. Presents extracellular protein derivatives for immune response | Has SNP with strong association with CLE (26)                                                    |
| IL10     | Cytokine produced by monocytes. Affects immunoregulation and inflammation and regulated JAK-STAT pathway.       | SNP associated with DLE but not SLE (23)                                                          |
| IRF5     | Transcription factor with roles in virus-mediated activation and regulation of cell growth, differentiation, apoptosis and immune activity | Polymorphisms in DLE three-fold greater than normal and five-fold greater than SLE (25). Significantly greater allele frequency in SLE compared to normal but no allele variation in DLE (24). |
| ITGAM    | Integrin important for adhering neutrophils and monocytes to endothelium | Two SNPs with nearly significant association to CLE are approximately ~36kB and 41kB upstream of the gene (26) |
| IZKF     | Protein involved with remodeling chromatin. Potential susceptibility gene for SLE | Believed to be associated with SNP ~27kB away that is strongly associated with CLE (26)          |
| MICA     | Stress induced cell surface protein recognized by delta T cells in the intestinal epithelium | SNP for this gene is strongly linked to another SNP associated with CLE (26)                     |
| MICA     | Stress induced cell surface protein which activates NK cells and CD8 T cells | Has SNP strongly associated with CLE (26)                                                        |
| MSH5     | Protein involved in mismatch repair associated with crossing over during meiosis. Also associated with radiation-induced apoptosis. | Cluster of 3 SNPs with strong association to CLE (26)                                             |
| RPP21    | Protein subunit of ribonuclease P. Processes 5′ head for tRNA.             | Mutation of the gene linked with familial chilblain lupus (20, 21)                               |
| SAMHD1   | Protein involved in innate immunity and response to infection. Plays a role in TNF-α signaling. | SNP of this gene has an association with both DLE and SLE compared to normal (24)                 |
| STAT4    | Transcription factor essential for mediating IL-12 response and helper T cell differentiation | Heterozygous gene mutation found in five family members with familial chilblain lupus (30)        |
| STING    | Transmembrane protein that is a major regulator of innate immune response to viral and bacterial infections | Two SNPs with frequencies in SLE patients two times greater than normal. No significant difference in DLE (27) |
| TLR7     | Toll-like receptor protein for pathogen recognition and activation of innate immunity | Greater allele variation in SCLE and SLE patients than DLE and normal patients (6, 22, 23)         |
| TNF      | Cytokine secreted by macrophages that regulates cell proliferation, differentiation and apoptosis | Significantly greater allele frequency in SLE compared to normal but no allele variation in DLE (24) |
| TNXB     | Glycoprotein associated with the extracellular matrix that functions in matrix maturation during wound healing | Novel SNP found in four siblings with DLE (28)                                                   |
| TRAF3IP2 | Protein involved with regulation cytokine response and plays a central role in innate immune response to pathogens, inflammation, and stress | Mutation of the gene linked with familial chilblain lupus (17–19)                                |
| TREGX1   | Protein associated with DNA polymerase proofreading. Has exonuclease activity that plays a role in DNA repair | Cluster of three SNPs with strong association to CLE (26)                                          |
| TRM39    | Protein of the tripartite motif family. Believed to have a role in apoptosis but not fully studied | SNP with increased risk of DLE but not SCLE (29)                                                 |
| TYK2     | Protein is part of JAK family. Is a component of type I and type III interferon signaling pathways | SNP with increased risk of DLE but not SCLE (29)                                                 |
TRIM39/RPP21) and previously described in SLE (i.e., HLA-DQA1, MICA/B, and IZKF) suggests unique and overlapping genetic underpinnings of CLE and SLE.

In summary, numerous genes were found to have SNPs that were associated with a greater risk of CLE and SLE, such as TLR7, TRAF3IP2, TYK2, IRF5, IL10, C1QA, and STAT4 (11, 23, 24, 27–29). Table 1 summarizes other additional genes whose polymorphisms are distinctly different in CLE and SLE groups (23, 24, 28–30).

**RNA**

Understanding the genetic aberrations at the DNA level serves as a foundation for examining the changes in the CLE transcriptome. The interplay of multiple pathways, namely, inflammation, apoptosis, and fibrosis, lays the framework for the pathomechanisms behind CLE (Figure 1). Herein, we describe the major contributors to CLE pathogenesis identified in gene expression analyses.

**UV Irradiation Is a Major Initiator in the Pathogenesis of Cutaneous Lupus Erythematosus**

UV irradiation has been thought to play a key role in the development of CLE, specifically due to the induction of autoantigens. After UV irradiation, nitric oxide is synthesized by nitric oxide synthases, such as inducible nitric oxide synthase (iNOS), and functions to protect cells, such as keratinocytes, from apoptosis (31, 32). Early work showed abnormal iNOS gene expression in the skin of patients with CLE patients who demonstrated delayed kinetics of iNOS induction by 72 h relative to controls (33). UVB irradiation induces chemokines, such as CXCR3 ligands CXCL9, CXCL10, and CXCL11, necessary to orchestrate the innate and adaptive response central to the immunopathogenesis of CLE (34). More recently, Katayama et al. (35) showed upregulation of the IFIT gene family, HLA-DPA1, and normal UV response genes (i.e., nucleic acid binding and eryhematous reactions) in CLE skin relative to healthy skin. The IFIT gene family has subsequently been shown to be the top hub genes in bioinformatics analysis of DLE skin (36). This inflammatory response is mediated by IFNs with greater concordant elevations in IFN-α levels in SCLE relative to DLE.

**Innate and Adaptive Immune Responses Drive Inflammation in Cutaneous Lupus Erythematosus Pathogenesis**

For many years, unfettered inflammation secondary to dysregulated Th1 axis has been understood to be at the heart of CLE pathogenesis. Early studies using reverse-transcriptase PCR identified the potential role of type 1 cytokines and inflammation pathways. Patients with DLE without SLE were found to have increased expression of IFN-γ and IL-2 (37). An examination of the T-cell cytokine profile in CLE showed an upregulation of IFN-γ but also IL-5, indicating a possible role for Th2 cells (38). In the context of the B7-CD28 pathway, the importance of T-cells in the pathogenesis of CLE is underscored by findings of B7-1 and B7-2 mRNA expression primarily in the dermis of patients with DLE, SCLE, and SLE (39). Microarray experiments comparing DLE to psoriasis confirmed a predominant Th1 signature and no Th17 signature, which is a hallmark of psoriasis (40). Bioinformatics analysis of gene networks notes an overlap of Th1 skewing of DLE with sarcoidosis (41). When CLE subtypes are compared, DLE and SCLE gene expression predominantly had a type 1 IFN signature, but DLE had a relatively increased expression of Th1-related cytokines (42).

Innate immune response functions upregulated by the Th1 phenotype include JAK/STAT signaling, toll-like receptor signaling, pattern recognition receptors, and antigen processing and presentation. Microarray and RNA-sequencing experiments consistently demonstrate upregulation of these inflammatory pathways in CLE skin (43–46). Recently, JAK/STAT upregulation in CLE has been the focus of targeted therapies, with JAK1-specific inhibition being explored as a promising approach for the treatment of CLE (47, 48). Enhanced toll-like receptor-dependent and pattern recognition receptor pathways contribute to both innate and adaptive immune responses in CLE (45). While often overlooked, only one study has examined the genome of CLE given the function of glycosaminoglycans in mediating inflammation by acting as pathogen-associated molecular patterns (49, 50). Upregulation of hyaluronan and chondroitin sulfate via HAS2 and CHSY1/CAST1, respectively, provides some evidence by which glycosaminoglycans participate in the characteristic inflammatory response of CLE. Finally, in a study by Zhu et al. (1), a unique machine learning approach leveraging modular analysis uncovered large heterogeneity in CLE, but central themes of Th1 dysregulation and interferon activation were largely preserved in identified clusters.

The adaptive immune response is also important in the pathogenesis of CLE via dysregulation in antigen presentation, activation of B-cells, and autoantibody production (36). Moreover, key players, such as IL-9 and B-cell activating factor (BAFF) may be important in CLE progression to SLE and the distinction of CLE from SLE. Elevated IL9 expression has been linked to production of autoantibodies in lupus-prone mice (51) and in skin of CLE patients who progressed to SLE versus those who did not (52). Similarly, our group found that higher BAFF mRNA and protein levels in patients with DLE versus those without SLE (53). Taken together, these findings suggest intricate interactions between the innate and adaptive immune response in mediating CLE pathogenesis and facilitating progression to SLE.

**Upstream Regulation Impacts the Degree of Inflammatory Signatures in Cutaneous Lupus Erythematosus**

Upstream mediators of inflammation have also been investigated. Spleen tyrosine kinase (SYK) is known to be a mediator of multiple innate and adaptive immune responses (54). Gene expression analysis via microarray of DLE (n = 7) and SCLE (n = 5) skin revealed upregulation of SYK and multiple SYK-regulated innate immune-related genes relative to healthy skin (n = 5) (55). Vorwerk et al. (56) postulate NKG2D, an immune receptor on NK cells and a subset of CD8 + T cells, contributes to CLE, giving upregulation on whole transcriptome RNA sequencing. However, NKG2D plays a selective role in autoimmune disease, and further mechanistic studies are
required to understand its role in CLE (57). Recent RNA-sequencing data of SLE skin have identified another transcription factor, PITX1, which facilitates hypersensitive responses to type I IFNs in lupus keratinocytes (58). Finally, RNA-sequencing analysis of long non-coding RNAs (IncRNAs) and circular RNAs (circRNAs) was differentially expressed in patients with DLE and correlated with inflammatory immune response-related genes on coding and non-coding gene network analysis (59). Further functional studies of IncRNAs and circRNAs are required to fully understand their biological function.

Upregulated Cytokines and Chemokines Enhance Inflammatory Response in Cutaneous Lupus Erythematosus

One member of the type I IFN family, IFN-α, has had a well-established signature within SLE patients with skin involvement (60). In CLE, IFN-α is upregulated in both lesional and non-lesional skin (61). IFN-α recently has been shown to promote the adherence of Staphylococcus aureus with CLE and SLE keratinocytes (62). Thus, in concert with dysregulation of barrier proteins, such as filaggrin, IFN-α has been mechanistically
implicated in the colonization of CLE lesions. In addition to IFN-α, IFN-κ has also been important in the dysregulation of CLE keratinocytes (58, 63, 64). Responsiveness to hydroxychloroquine therapy has been associated with an increased type I IFN signature, while high TNF-α was associated with response to adjunct quinacrine (2).

Upregulated expression of chemokines CXCL9, CXCL10, and CXCL11 and its receptor CXCR3 is a hallmark of CLE (65). These chemokines exert their effect on CXCR3-expressing cells and orchestrate the Th1 immune response by promoting Th1 cell migration (34, 48, 66). These chemokines have been repeatedly shown to facilitate interface dermatitis (66). CXCL9 and CXCL10 expression were strongly correlated with IFN-γ expression in DLE (n = 15), SCLE (n = 11), and LET (n = 21) skin. (67). Novel bioinformatics approaches have shown that these chemokines as key genes are involved in CLE (68).

**Apoptosis Perpetuates Inflammation**

Apoptosis is broadly comprised of the extrinsic and intrinsic pathways. Current evidence suggests increased activity of the extrinsic apoptotic pathway via the upregulation of the TRAIL receptor system and CD95 (69, 70). Specifically, an increase of apoptotic keratinocytes has been observed in CLE with concomitant increased epidermal expression of TRAIL-R1, CD95, and FADD (64, 69). Apoptotic keratinocytes contribute to the pathogenesis of CLE via the release of cellular debris, which results in a positive feedback loop of inflammation. Recent work by Kingsmore et al. (71) noted increased apoptotic mitochondrial gene signatures in DLE and lupus nephritis, suggesting a role for the intrinsic apoptotic pathway, and positive correlation with inflammatory cell signatures supports the intrinsic link of apoptosis with inflammation. Gene set expression analysis with microarray and RNA-sequencing of CLE skin and blood identified other genes, such as GZMB, BAX, and various caspases (CASP8/10) among others (1, 64, 72–75). Differential expression analysis of CLE lesional skin and blood skewed toward lesional skin, though apoptosis signatures were noted in both environments. Apoptosis and necroptosis pathways via RIP3 are activated in interface dermatitis characteristic in CLE (76).

Downregulation of anti-apoptotic genes has also been identified in CLE. RANKL, a regulator of apoptosis, is notably absent from CLE skin (77). While TRAIL-R1 has been shown to be pro-apoptotic, TRAIL-R4 serves as a decoy receptor, blocking TRAIL-induced apoptosis, and has been shown to be downregulated in CLE relative to psoriasis and lichen planus (69, 78).

**Complements, Lysosomes, and Proteosome Contribute to Impaired Clearance of Cell Debris in Cutaneous Lupus Erythematosus**

The complement cascade plays a pivotal role in the opsonization of cells undergoing apoptosis to facilitate phagocytosis, and the timely clearance of cellular debris is important to prevent the generation of autoantibodies. Similarly, lysosomal and proteosomal clearance of cellular debris via proteolysis plays an important role and has been shown to be dysregulated in CLE. Skin gene expression of complement has been shown to be more dysregulated relative to blood gene expression in CLE (74, 79, 80). This is contrasted with the upregulation of cathepsins associated with lysosomes and proteasome-related genes in CLE peripheral blood relative to lesional skin (35, 74). The complex dysregulation of the systems involved in the clearance of cellular debris at a localized and systemic level highlights the complexity of the pathogenesis of CLE.

**Fibrosis Is Likely Driven by TGF-β in Cutaneous Lupus Erythematosus**

Of the CLE subtypes, DLE has been most associated with scarring lesions with associated fibrosis. Comparison of patients with DLE and SCLE using Ingenuity Pathway Analysis revealed pathways associated with fibrotic processes, and longitudinal microarray analysis of patients with DLE and SCLE revealed sustained elevations of TGF-B1, TGF-BR1, SMAD3, MMP1, MMP9, and SERPINE1 (42). Interestingly, while TGF-β, a M2 macrophage-related protein, was noted to be overexpressed in DLE skin relative to normal skin in an independent experiment, other M2 macrophage-related genes, such as CD206, CD209, FOLR2, IL10, and arginase-1, were not differentially expressed (65). Taken together, TGF-β likely plays a key role in fibrogenesis in scarring DLE lesions, though the exact downstream mechanisms have yet to be fully defined.

**CONCLUSION**

Our understanding of the underlying genetics governing the pathophysiology of CLE has greatly increased, thanks to advances in gene expression technology. Insights into the underlying genetic polymorphisms that predispose patients to CLE and knowledge of key dysregulated pathways in CLE afford the opportunity to develop targeted therapies for patients with CLE. Most recently, pathogenesis-directed therapy has focused on blockade of IFN receptors, such as anifrolumab (81). Other approaches, such as targeting the JAK/STAT pathway, are under investigation (82–84). The limitations of reviewed studies include small sample size, specific, non-generalizable cohorts, and technical limitations of gene expression profiling approaches, such as low resolution in microarray studies. Further studies using newer technologies, such as single-cell RNA sequencing, are warranted to define the genetic pathophysiology of CLE at greater resolution. Greater understanding of the underlying genetics of CLE can lead to further development of targeted therapies for CLE.

**AUTHOR CONTRIBUTIONS**

HC and BC conceived and designed the study. HC and GB acquired, analyzed, interpreted the data, and drafted the original manuscript. All authors contributed to critical revision of
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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.916011/full#supplementary-material

**Supplementary Figure 1** | Flow diagram of workflow for the literature review.
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