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Cutaneous and Systemic Connections in Lupus

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Abstract

Purpose of Review—Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multiple manifestations, with a majority of SLE patients having cutaneous involvement. Despite ongoing research, the relationship between SLE and cutaneous lupus erythematosus (CLE) pathogenesis remains unknown. This review will compare advances in understanding the etiology and pathogenesis of SLE and CLE.

Recent Findings—Recently, mechanisms by which immune cell populations contribute to the pathogenesis of SLE and CLE have been queried. Studies have pointed to transitional B cells and BAFF signaling as potential drivers of SLE and CLE, with belimumab clinical data supporting these hypotheses. Ustekinumab trials and an exciting Treg adoptive transfer in an SLE patient with cutaneous disease have suggested a role for T cell-targeted therapies. The theory that neutrophil NETs may be a source of autoantigens in SLE remains controversial, while neutrophils have been suggested as early drivers of cutaneous disease. Finally, plasmacytoid dendritic cells (pDCs) have been studied as a potential therapeutic target in SLE, and anti-BDCA antibody clinical trials have shown promise in treating cutaneous disease.

Summary—While recent findings have contributed to understanding SLE and CLE pathogenesis, the mechanistic link between these diseases remains an area requiring further research.

Keywords

Systemic lupus erythematosus; cutaneous lupus erythematosus; B cell; T cell; Neutrophil; plasmacytoid dendritic cell

INTRODUCTION

Systemic lupus erythematosus is a heterogeneous autoimmune disorder with multiple manifestations, including skin, joint, and kidney inflammation, that is characterized by production of autoantibodies and circulating immune complexes (1). Up to 70% of SLE patients have cutaneous involvement (2), while progression from CLE to SLE occurs in

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approximately 20% of patients diagnosed with CLE as a presenting symptom (3). CLE can also exist independently without systemic disease (4). Despite ongoing research, the mechanistic links between CLE and SLE remain unknown. This review aims to examine recent updates of CLE pathogenesis and its relationship to SLE and how recent advances in specific therapies for CLE and SLE inform this connection.

CLE CLASSIFICATION

Cutaneous lupus erythematosus refers to a broad spectrum of lesions which can be classified into the following categories: Acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), chronic cutaneous lupus erythematosus (CCLE) (4).

ACLE refers to perhaps the most classically recognized cutaneous manifestation of SLE - the malar or “butterfly” rash - which presents in sun-exposed areas and often resolves without scarring (5). Like ACLE, SCLE lesions present on sun-exposed skin and are annular or with a psoriasiform appearance (5). SCLE is also associated with presence of anti-SSA and anti-SSB antibodies (5, 6), and SCLE represents the most common form of drug-induced lupus (5, 7). Finally, CCLE makes up about 80% of CLE lesions, making it the most common subtype of CLE (5). CCLE is comprised of a number of subtypes of its own, including lupus erythematosus profundus, chilblain lupus, LE tumidus, and most commonly, discoid LE (DLE) (4, 5). DLE lesions can present as localized or diffuse lesions and, when localized, are often observed on the scalp, face, or ears (5). Upon resolution, DLE lesions often leave disfiguring scars and hyperpigmentation (5). Notably, new classification criteria for DLE have just been validated (*8).

RELATIONSHIP BETWEEN CLE and SLE

In SLE, skin is the second most frequent site affected at initial presentation and overall represents the second most commonly affected organ (9, 10). While the exact mechanisms governing the link between CLE and SLE have not been identified, some prognostic differences have been suggested between different CLE subtypes. SLE patients who present with ACLE may have more severe systemic symptoms, while DLE patients are less likely to have nephritis within five years of SLE diagnosis compared to SLE patients without CLE (9, 11). These findings highlight the importance of understanding the relationship between CLE and SLE pathogenesis—a task complicated by the heterogeneity of CLE phenotypes and thus potentially distinct pathogeneses of CLE subtypes.

MECHANISMS OF DISEASE

SLE and CLE pathogenesis are complex and influenced by environmental factors, genetic predisposition, and inherent dysfunction of immune cells. Here, we review recent literature regarding B cells, T cells, dendritic cells, and neutrophils in SLE and CLE.

B CELLS

B cells have long been regarded as pathogenic drivers of SLE. Loss of B cell tolerance in lupus leads to production of autoantibodies against self-antigens such as self-DNA, red blood cells, phospholipids, and histones (12). Multiple mechanisms have been proposed to

explain this loss of tolerance including increased cell apoptosis and subsequent defective clearance of apoptotic cell debris (13). Recent data point to disruptions in tolerance checkpoints during B cell development, particularly at the transitional B (TrB) cell stage, which allows for survival and proliferation of autoreactive B cells (*14). TrB cells have been found to be increased in the blood SLE patients when compared with healthy controls (*14, 15, *16), and several studies have demonstrated intrinsic dysfunction of these TrB cells that support autoreactivity, including a strong IFN signature even in clinically quiescent patients (*14), decreased expression of CD19 and CD21 (*14, 15), and defects in TLR9 signaling (14, 15). In accordance with these data, Mei Liu *et al.*, showed that plasma from Chinese SLE patients supported TrB cell survival in a type I IFN-dependent fashion and that SLE TrB cells produce more IL-6, which positively correlated with SLE disease activity in these patients (*16). In line with these findings, levels of the B cell activating factor BAFF, a regulator of TrB cell development and survival (17, 18), are increased in SLE patients (19). In a recent study of SLE patients taking belimumab, a BAFF inhibitor, Huang *et al* showed that BAFF inhibition leads to a negative selection of autoreactive activated B cells (17). Taken together, these data suggest a role for TrB cells as early drivers of SLE pathogenesis.

Unlike SLE, B cell involvement in cutaneous lupus has been more controversial. However, some studies have suggested a role for BAFF in CLE lesions. Staining of BAFF has been reported in the epidermis in DLE lesions at levels higher than in healthy controls and psoriasis lesions (20). More recently, BAFF expression was evaluated in the epidermis of several subtypes of CLE. The highest BAFF expression was noted in SCLE, DLE, and lupus profundus (21). Interestingly, treatment of cultured keratinocytes with immunostimulatory DNA that mimic drivers of CLE lesional inflammation demonstrated an increase in keratinocyte BAFF expression (21). Indeed, belimumab, a BAFF inhibitor, is currently in phase III clinical trials for efficacy in treatment-resistant CLE (22), and other studies have reported improvement in cutaneous disease with belimumab treatment (*23, 24). Overall, these data suggest a role for B cells in CLE pathogenesis, but whether B cells serve as a link between skin and systemic symptoms remains unclear.

T CELLS

T cells have been demonstrated to contribute to SLE pathogenesis through secretion of pro-inflammatory cytokines, providing help to B cells, and inducing cytotoxicity of keratinocytes in the case of CD8⁺ T cells in CLE (25, 26, 27). IFN γ -producing CD8⁺ T cells (along with myeloid and natural killer cells) have also been identified as central to chemokine production associated with driving inflammation in lupus nephritis (**28). CD4⁺ Th17 cells make IL-17F and IL-17A, and increased quantities of Th17 cells have been found in the circulation of SLE patients as well as lupus-prone mice, which positively correlated with disease activity (29, 30, 31). Interestingly, depletion of IL-17 in the Roquin^{san/san} mouse model of lupus showed decreased disease activity including promotion of Treg differentiation, decreased Tfh differentiation, and decreased autoantibody production (*32). The transcription factor STAT3 regulates expression of IL-17, and it has been shown that STAT3 expression is also increased in SLE patients (33, 34, 35) as well as lupus prone mice (36). Use of a small-molecule STAT3 inhibitor in the MRL/lpr lupus-prone mouse model has been shown to decrease autoantibody titers and delay onset of proteinuria (37). T-cell

specific silencing of STAT3 has been shown to decrease T cell help to B cells, leading to decreased autoantibody production and abrogated nephritis (38). In line with these data, use of JAK inhibitors, which inhibit kinases upstream from STATs, has been tested in SLE. Tofacitinib, which primarily inhibits JAK1 and JAK3, has been shown to improve disease in lupus prone mice (39), and a phase IIb trial of baricitinib, another JAK inhibitor, has shown promising results in treating SLE that was not well controlled on standard therapies (40).

The Treg/Th17 balance has been queried in CLE pathogenesis as well with controversy in the results. Some studies have shown an increase in Th17 cells in DLE lesions (41) and a correlation between IL-17 and IFN α in CLE lesions (42), while others have argued no increase in Th17 but rather an increase in Th1 cells in DLE lesions (43). Interestingly, a phase II trial of ustekinumab, an IL-12 and IL-23 inhibitor, showed a significant improvement in skin disease in >60% of patients who were treated, and this effect was sustained over 52 weeks (**44, 45). Whether the effects of ustekinumab are secondary to effects of IL-12 or IL-23 or both remains to be determined. Foxp3+ Treg cells have been shown to be decreased in CLE lesions compared to other inflammatory skin conditions (46), and UVB exposure in lupus-prone mice has shown a decrease in Treg differentiation, which increases effector T cell activation in skin draining lymph nodes (*47). Interestingly, a recent study with one CLE patient treated with autologous polyclonal Tregs adoptive transfer, which showed that the transferred Tregs homed to lesional skin and maintained stable disease without any CLE flares over a 24-week follow up period (*48). In another study, expansion of Tregs using low-dose IL-2 has shown promise in both murine and human studies (49). Ongoing trials for IL-2 therapy to boost Treg function in SLE and CLE patients will be informative regarding the role of Tregs in disease. Together, these data suggest that dysfunctional Tregs may be implicated in CLE pathogenesis and Treg directed therapies could alleviate CLE disease manifestations.

NEUTROPHILS

Neutrophils are important to the pathogenesis of SLE. SLE patients have been shown to have an increased subset of abnormal neutrophils called low-density granulocytes (LDG) which produce and release excess neutrophil extracellular traps (NETs) as a source of defense in a process called NETosis (50). In NETosis, a neutrophil encounters an “invader” and releases a web of chromatin, genetic material, and various proteolytic enzymes to trap and degrade the invader (51). While this process aids in host defense, it can also drive pathogenesis of autoimmune disorders like SLE (52, 53). Serum from SLE patients has been shown to induce neutrophil NET formation (54, 55). NETs have been hypothesized to provide a source of autoantigens in SLE pathogenesis, and indeed in one study, antibodies against NETs were identified in 36% of SLE patients (56). Recent data has supported this theory, showing that LL37-DNA complexes within NETs can trigger autoantibody production by memory B cells (*57) and that SLE immune complexes can drive NET formation (55). However, this hypothesis is not without controversy, as others have recently suggested that disrupting critical mediators of NETosis and thus inhibiting NETs in lupus-prone mice has little bearing on SLE pathogenesis (58, 59, 60). Further investigation is warranted to understand the contribution of NETs to SLE pathogenesis.

There is also evidence for involvement of NETs in CLE lesions. LDGs are associated with CLE skin lesions, and NETs are found in CLE lesions (50, 61). In a recent study using a murine CLE model with deletion of PD-1H, neutrophils were found in the skin before disease onset, implicating them in initiation of CLE lesions (62). Different subsets of CLE have been shown to have differential expression of NETs, with DLE and ACLE lesions exhibiting higher NET expression than SCLE lesions (63). Intriguingly, UV light can also induce NETosis (64), which may provide a pathogenic link between UV exposure and CLE. Whether neutrophils link CLE to systemic disease is not known.

PLASMACYTOID DENDRITIC CELLS

Plasmacytoid dendritic cells (pDCs) are a subset of dendritic cells that are specialized to produce type I IFN after TLR7- and 9-mediated recognition of viral or self-nucleic acids and subsequent activation (65). Besides type I IFN production, pDCs can present antigens to CD4⁺ T cells and also secrete other pro-inflammatory molecules including BAFF, TNF α , and IL-6 (65). Depletion of pDCs in murine models of lupus has been shown to ameliorate autoimmunity (66, 67). As such, targeting pDCs has been an attractive potential therapeutic option for SLE. CXCR4 has been identified as a potential regulator of pDC activation (68), and recently, a small molecule ligand of CXCR4 has been identified as a potent TLR7 inhibitor with the ability to inhibit pDC activation (69). Administration of this small molecule in a TLR7-driven murine lupus model revealed decreased anti-dsDNA antibodies and prevention of nephritis, while treatment of cells from SLE patients with this small molecule showed decreased IFN α secretion (69). These data suggest an important role of pDCs in SLE pathogenesis and an interesting potential pDC-targeted SLE therapy.

As in SLE, pDCs may be important in CLE pathogenesis as well. It has been demonstrated that pDCs are present in CLE lesions but not normal skin (70). These data have recently been supported by a study showing that DLE patients exhibited higher numbers of pDCs in lesional skin when compared with lichen planopilaris (71). Ultraviolet (UV) radiation is a known trigger of CLE lesions, and pDCs have been shown to home to the skin of UV-irradiated lupus-prone mice at higher rates than wild type mice; this finding has also been corroborated in humans (72, 73). These recruited pDCs produce IFN- α and are a potential source of type I IFN signaling in CLE (74, 75). These type I IFNs go on to upregulate cytokines, chemokines, and adhesion molecules which recruits and then activates more pDCs and other inflammatory cells (76, 77). Additionally, SLE keratinocytes irradiated with UVB can activate DCs through IFN signaling, which can augment the inflammatory response to UVB (78). In alignment with these data, a recent phase I trial using a monoclonal antibody against BDCA2, a pDC specific receptor involved in type I IFN production, has shown benefit in treating CLE lesions (**79). In total, these data suggest that pDCs may play important role in CLE pathogenesis.

MECHANISTIC LINKS BETWEEN SYSTEMIC AND CUTANEOUS LUPUS

While the exact mechanisms connecting cutaneous disease and greater systemic involvement is still poorly understood, some advances have been made in understanding how skin inflammation can lead to systemic disease. In 1997, Seery *et al* showed that overexpression of IFN γ in murine epidermis can lead to production of autoantibodies and subsequent

development of autoimmunity (80). More recently, Clark *et al* identified a new murine model of systemic lupus triggered by epidermal injury through tape stripping, mirroring evidence in human lupus that cutaneous triggers can trigger systemic disease (81). Following epidermal injury, they found evidence of epidermal neutrophilic inflammation followed by immune complex deposition in the kidney and transcriptional changes in type I IFN response genes and chemokines that support development of nephritis (81). Interestingly, the same study showed that while epidermal injury in BALB/c mice didn't cause nephritis, it did lead to increased anti-dsDNA antibody titers in injured versus non-injured mice, suggesting that epidermal injury can contribute to autoimmunity in wild type mice as well (81). Similarly, another study using TLR7 agonists to stimulate cutaneous inflammation and nephritis showed that only topical and not systemic TLR7 agonists were sufficient to induce disease (82). Further evidence for this skin->systemic inflammation concept is found in the murine model in which the female-biased transcription factor *Vgll3* is overexpressed in the epidermis of B1/6 mice (**83). These mice get a robust CLE phenotype, B cell activation, IFN upregulation, and immune complex deposition in the kidney (83). Intriguingly, in wild type mice, a large, single UV exposure is sufficient to induce a rapid, systemic cGAS-dependent interferon response, suggesting that inflammatory changes in the skin quickly translate to systemic IFN responses (**84). There is also some evidence in humans that the IFN response in the skin can reflect renal IFN activation (85). Taken together, these data implicate the skin as one potential site of triggering systemic disease.

CONCLUSION

As reviewed, recent advances in SLE and CLE research have identified immune populations implicated in pathogenesis of both diseases and the mechanisms by which they contribute to phenotype (Figure 1). Ultimately, while these advances have aided in the larger understanding of SLE and CLE pathogenesises individually, more data is needed to understand the exact mechanisms and cell populations involved that connect the skin with systemic disease.

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KEY POINTS

- SLE is a heterogeneous autoimmune disorder with a significant portion of patients having cutaneous manifestations, although CLE can exist on its own without systemic disease.
- Transitional B cells and BAFF signaling are potential drivers of SLE and CLE.
- Increased IL-17-producing Th17 cells and decreased Tregs in SLE contribute to nephritis, while autologous Treg transfer in a CLE patient has shown promise for treating cutaneous disease.
- UV light has been shown to induce neutrophil NETosis, which may provide a source for autoantigens in SLE.
- Plasmacytoid dendritic cells home to the skin after UV exposure and provide a source of type I IFN in CLE lesions, while new pDC targeted therapies are being studied for both SLE and CLE treatment.

FIGURE 1.

CLE lesions are known to be triggered by UV light, which causes keratinocyte apoptosis. In the setting of dysfunctional clearance, this apoptosis allows for persistence of extracellular self-DNA which contributes to IFN production, T cell activation via antigen presentation, and B cell-mediated autoantibody production. UV light triggers neutrophil NETosis, which could represent another source of immunogenic self-DNA. pDCs home to the skin following UV exposure and are a source of type I IFNs in the skin, which contributes to disease pathogenesis.

Like CLE, SLE is characterized by increased apoptosis and defective clearance mechanisms leading to immune complex formation against self-DNA and nuclear materials. SLE immune complexes promote neutrophil NETosis, which has been shown to directly activate B cell autoantibody production through LL37-DNA complexes. These immune complexes also activate pDCs to produce inflammatory cytokines that contribute to TrB cell survival and IL-6 production. Given this cytokine milieu, CD4 T cell populations become enriched in IL-17-producing Th17 cells with fewer Tregs in circulation, which has been shown to contribute to worsening nephritis. Similarly, IFN γ -producing CD8+ T cells have also been shown to contribute to SLE nephritis.