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Pathogenesis of Scarring in Cutaneous Lupus Erythematosus: A Focus on Discoid Lupus Erythematosus

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ABSTRACT: Background: Scarring, particularly in discoid lupus erythematosus (DLE), is an irreversible complication of cutaneous lupus erythematosus (CLE). Current treatments can control inflammation but may not prevent established tissue damage.

Objective: To summarise current evidence on the mechanisms of fibrosis and scarring in CLE, with emphasis on DLE.

Methods: This narrative review draws on targeted searches of PubMed, Scopus, and Web of Science, as well as reference lists of relevant publications. The literature was qualitatively synthesised, focusing on immune-mediated injury, basement membrane zone alterations, fibroblast signalling, and hair follicle stem-cell compartments.

Results: Studies in DLE support contributions from persistent type I interferon signalling and cytotoxic lymphocytes to epidermal and follicular injury. Histopathologic studies describe basement membrane zone abnormalities and perifollicular inflammation, while molecular studies implicate transforming growth factor-β-related signalling and extracellular matrix remodelling. Studies of cytokeratin 15 indicate involvement of the hair follicle bulge compartment. However, the causal role of stem-cell loss and the relevance of hypoxia, epigenetic changes, and other profibrotic pathways in CLE remain incompletely defined; some evidence is extrapolated from systemic lupus erythematosus or other fibrotic diseases.

Conclusion: Scarring in DLE likely reflects interacting immune injury, structural damage, and impaired repair. Further CLE-specific studies are needed to establish these mechanisms and identify strategies to prevent permanent scarring.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a heterogeneous group of autoimmune skin disorders with clinical presentations that vary in morphology and distribution; it may occur as skin-limited disease or in association with systemic lupus erythematosus (SLE) (1–4). Among chronic CLE subtypes, discoid lupus erythematosus (DLE) is particularly associated with permanent scarring and dyspigmentation, which may persist after visible inflammation subsides (1–5).

The impact of DLE extends beyond visible lesions. Permanent scarring, particularly on the scalp and face, can cause lasting cosmetic changes and may adversely affect quality of life (5,6). A disease-specific quality-of-life measure has been validated in patients with CLE, highlighting the importance of assessing this broader burden (6). Current therapies, including antimalarials and corticosteroids, are used to control active inflammation (7); however, established scarring may not be reversible, making early disease control important to limit further damage.

Despite progress in understanding the immunopathogenesis of CLE, the mechanisms linking chronic inflammation to irreversible tissue damage and scarring remain incompletely defined. Recent studies have linked scarring DLE to persistent immune signalling and profibrotic responses in dermal fibroblasts, but how these processes interact with epidermal and follicular injury remains unclear (8,9).

Accordingly, this narrative review synthesises current evidence on how chronic immune-mediated injury may lead to fibrosis and permanent scarring in cutaneous lupus erythematosus (CLE), with particular emphasis on discoid lupus erythematosus (DLE). It examines the interplay among immune-cell activity, basement membrane zone disruption, dermal fibroblast activation, and changes in hair follicle stem-cell compartments, and discusses the clinical implications and key gaps requiring further investigation.

METHODOLOGY

This narrative review was based on targeted searches of PubMed, Scopus, and Web of Science for English-language publications. Search terms included "cutaneous lupus erythematosus," "discoid lupus erythematosus," "fibrosis," "scarring," "basement membrane zone," "hair follicle stem cells," "fibroblast activation," and "extracellular matrix remodelling." Additional relevant articles were identified by manually reviewing the reference lists of selected reviews and original studies. Publications were selected based on their relevance to the clinical, histopathological, cellular, or molecular mechanisms of fibrosis and scarring in CLE, and on their scientific quality. Recent studies providing mechanistic insights were prioritised, while earlier landmark studies were included when relevant for background. Study selection did not follow a prespecified systematic-review protocol. The literature was synthesised qualitatively to examine links among chronic inflammation, structural tissue injury, impaired regeneration, and fibrotic remodelling in CLE, with particular emphasis on DLE.

Pathogenesis of Scarring in CLE

Scarring in cutaneous lupus erythematosus (CLE), particularly discoid lupus erythematosus (DLE), develops through the interaction of persistent inflammation, structural tissue injury, and impaired repair. Rather than being a passive consequence of injury, scarring involves progressive fibroinflammatory activity and tissue remodelling (8–12). Several interconnected processes may contribute to this progression, including dermal fibroblast activation and extracellular matrix deposition, basement membrane zone (BMZ) disruption, and alterations in hair follicle stem-cell compartments that may limit regenerative capacity (9,13,14). This section examines three related areas: (1) chronic inflammation and fibroblast activation; (2) BMZ disruption and associated changes in the hair follicle stem-cell niche; and (3) profibrotic molecular signalling and dermal remodelling. Relevant clinical and histopathological findings are discussed within these sections.

Chronic inflammation and fibroblast activation

Scarring is most characteristic of chronic cutaneous lupus erythematosus (CLE), particularly discoid lupus erythematosus (DLE). Immunohistochemical studies of scarring DLE lesions have identified increased numbers of granzyme B–positive cytotoxic lymphocytes together with strong expression of MxA, a marker induced by type I interferons. These findings support an association between interferon-related immune activity and cytotoxic inflammation in scarring DLE, although they do not establish that these processes directly cause permanent scarring (15,16).

Histologically, DLE commonly shows inflammatory infiltrates involving the pilosebaceous units, whereas inflammation in subacute cutaneous lupus erythematosus (SCLE) is generally more superficial and less often associated with permanent scarring (17,18).

Line-field confocal optical coherence tomography (LC-OCT) has been reported to visualise periadnexal inflammatory features in a DLE lesion, with findings corresponding to histopathology in that case (20). Although LC-OCT may provide non-invasive in vivo imaging, its diagnostic accuracy and role in monitoring disease activity or reducing the need for biopsy in DLE remain unestablished, and further studies are needed (19,20).

The inflammatory environment in CLE involves interactions between innate and adaptive immune cells. Plasmacytoid dendritic cells accumulate in cutaneous lupus lesions and are associated with type I interferon activity (21). In SLE, macrophage activation profiles have been associated with disease activity (22). Separately, dermal fibroblasts in scarring lupus skin exhibit a profibrotic

phenotype, with TGF-β implicated in fibrotic responses (9). Together, these findings suggest that persistent immune activity and profibrotic fibroblast responses may contribute to scarring in DLE.

Granzyme B and cytotoxic T-lymphocyte activity have also been investigated in systemic lupus erythematosus (SLE) (23). However, these systemic findings do not demonstrate that granzyme B directly induces apoptosis of follicular stem cells in DLE. Transcriptomic studies have characterised immune-cell populations and inflammatory gene-expression patterns in lupus skin lesions (24,25). MxA has also been proposed as an additional histological marker in suspected CLE, reflecting type I interferon activity (26).

Evidence supports a role for profibrotic signalling in DLE. A gene-expression study identified a transforming growth factor–β (TGF-β)-related fibrosis signature in DLE, while broader fibrosis research provides context for the potential effects of TGF-β on extracellular-matrix production (27,28). Experimental studies have linked hypoxia-induced HIF-1 signalling to fibrogenesis and extracellular-matrix remodelling in noncutaneous models (29), while HIF-1α has also been investigated in relation to fibrosis and extracellular-matrix remodelling in CLE (30). However, direct evidence establishing this pathway in DLE remains limited (29,30). Matrix metalloproteinase activity has also been investigated in CLE and may influence tissue injury and matrix turnover, although its precise contribution to progressive fibrosis remains unclear (31). Hair-follicle stem cells in the bulge contribute to follicular regeneration (32). CLE-specific studies have described involvement of the bulge region in DLE, suggesting that injury to this compartment may contribute to permanent follicular loss (14). However, the available evidence does not establish that granzyme B directly induces apoptosis of these stem cells in DLE. Epigenetic mechanisms have been discussed in systemic lupus and other autoimmune diseases (33,34). Their role in maintaining fibroblast activation and fibrosis specifically in DLE remains an area for further study.

Overall, the evidence reviewed in this section suggests that scarring in DLE may involve interacting immune, structural, and profibrotic processes, although the contribution of some pathways remains incompletely defined. Table 1 summarises the proposed pathogenic drivers and their potential clinical implications, while Table 2 outlines the major cellular and molecular interactions discussed in this section.

Basement Membrane Zone Disruption in CLE

The basement membrane zone (BMZ) forms the interface between the epidermis and dermis and is a site of histopathologic change in cutaneous lupus erythematosus (CLE). Histopathologic comparison has identified thickening around pilosebaceous structures as a feature favouring discoid lupus erythematosus (DLE) over subacute cutaneous lupus erythematosus (SCLE) (35,36). In patients with systemic lupus erythematosus (SLE), reduced expression of heparan sulphate proteoglycan has been reported in the skin BMZ (37). Direct immunofluorescence studies have also described immune-reactant deposition along the BMZ in cutaneous and systemic lupus (38). These findings support BMZ involvement in lupus, but the SLE findings alone do not establish the same molecular alterations in DLE.

Immunohistochemical analyses have demonstrated altered expression of basement membrane zone components, including laminin 5 and type IV collagen, in active DLE lesions (13). Alterations in basement membrane zone proteins have also been described in lichen sclerosus (39). Laminin is a basement membrane glycoprotein (40), while hemidesmosomes contribute to the adhesion of basal keratinocytes to the basement membrane zone (41). Together, these findings suggest that altered basement membrane organization may weaken dermoepidermal adhesion and contribute to tissue damage in chronic CLE. However, a direct causal role in permanent scarring has not been established (13,39–41).

By contrast, SCLE generally shows less pronounced BMZ alterations than DLE. Histopathologic and immunohistochemical studies have reported BMZ thickening around pilosebaceous structures and altered expression of BMZ components in active DLE, whereas SCLE shows fewer such changes (13,35). Direct immunofluorescence literature has also described immune-reactant deposition at the BMZ in cutaneous and systemic lupus (38). Laminin is a basement membrane glycoprotein (40). These findings support BMZ involvement in lupus, but do not establish that BMZ alterations directly impair keratinocyte regeneration or cause ongoing tissue damage. In active DLE, immunohistochemical analyses have reported increased expression of the hemidesmosome-associated proteins BP230 and plectin (13). Hemidesmosomes contribute to basal keratinocyte adhesion at the dermoepidermal junction (41), although the cited evidence does not establish that these expression changes cause basal-cell apoptosis. Altered signalling and autoantibodies have been discussed in the CLE and lupus literature (42,43), but these sources do not establish that antibodies targeting laminin-5 or type VII collagen drive BMZ injury in DLE. The

proposed role of adhesion molecules in retaining immune cells at the dermoepidermal junction should therefore be presented as a possibility requiring further study (42).

Comparative studies suggest that DLE and lichen planopilaris (LPP), although both associated with scarring alopecia, show differences in the distribution and pattern of tissue injury. In DLE, immune deposits along the basement membrane zone (BMZ) may be detected by direct immunofluorescence, whereas LPP is characterised by abnormalities involving the follicular BMZ and bulge region (44,45). BMZ disruption may contribute to tissue remodelling and fibrotic responses in DLE. A gene-expression study identified a TGF-β-related fibrosis signature in DLE lesions, although it did not establish that BMZ breakdown directly activates dermal fibroblasts (28). LC-OCT has been reported to visualise BMZ and adnexal changes in an active DLE lesion; its diagnostic role requires further evaluation (20). Direct immunofluorescence is used to assess immunoreactant deposition along the BMZ in cutaneous lupus, but the cited evidence does not establish that such deposition consistently correlates with persistent inflammatory infiltrates (38).

Proteolytic enzymes, including matrix metalloproteinases (MMP-1 and MMP-9), contribute to degradation of laminin and type IV collagen, thereby destabilizing the dermoepidermal interface and facilitating immune cell infiltration and keratinocyte injury (31). This proteolytic activity may also release latent TGF-β, while hypoxia-induced HIF-1α enhances expression of profibrotic genes. Together, these mechanisms reinforce extracellular matrix accumulation and sustain chronic fibrosis (30,31).

Overall, BMZ disruption in DLE should be regarded as an active pathogenic process rather than a passive histologic feature. Through a combination of structural damage, autoimmune targeting, and proteolytic degradation, BMZ alterations contribute to the development of a profibrotic microenvironment that perpetuates immune activation and scarring. Collectively, these findings support the BMZ as both a diagnostic indicator and a potential therapeutic target in scarring forms of CLE.

Dermal Remodeling and Fibrotic Molecular Signatures

Dermal fibrosis in discoid lupus erythematosus (DLE) involves changes in the dermal stromal compartment and activation of profibrotic pathways. Solé et al. identified increased fibrotic markers and evidence of TGF-β pathway activation in DLE lesions, supporting a role for TGF-β-related signalling in DLE fibrosis (28). More recently, Shoffner-Beck et al. found that lupus dermal fibroblasts exhibit heightened inflammatory responses, while fibroblasts from patients with scarring cutaneous lupus showed increased collagen-related responses to TGF-β. Their findings support a potential contribution of fibroblast activation to tissue fibrosis in scarring lupus, although further work is needed to clarify how these responses lead to irreversible remodelling (9).

From a histopathologic standpoint, DLE lesions may show basement membrane thickening, epidermal atrophy, and pilosebaceous atrophy or loss. In comparison, SCLE generally shows less pilosebaceous damage and typically heals without scarring (35,36). These differences are consistent with the more prominent scarring phenotype of DLE.

The TGF-β/Smad pathway is an important axis of fibrogenesis. Other signalling pathways, including Wnt/β-catenin, IL-6/STAT3, and Toll-like receptor pathways, have also been implicated in inflammation and fibrosis across autoimmune diseases (47). Their specific contributions to fibroblast activation and extracellular-matrix production in DLE, however, remain to be established. The possible interaction among these pathways may help explain persistent profibrotic activity and warrants further investigation.

Notably, parallels may be drawn between DLE and other autoimmune fibrosing conditions, including systemic sclerosis (SSc). In SSc, TLR8 activation has been shown to promote skin fibroblast activation and increase inflammatory and profibrotic responses, including IL-6 and collagen expression (48). These findings provide a potential comparison for DLE; however, a similar role for TLR8 in DLE has not been established. HIF-1 has been implicated in pathogenic cytotoxic T-cell responses in lupus skin, but its direct contribution to fibroblast activation and fibrosis in DLE remains unclear (49). Oxidative stress and reactive oxygen species have also been discussed in the pathogenesis of systemic lupus erythematosus (50). Their specific contribution to extracellular-matrix deposition, keratinocyte apoptosis, and scar formation in DLE requires further investigation.

Findings from transcriptomic studies support an association between inflammatory signalling and profibrotic activity in DLE. TGF-β-related fibrotic signalling has been reported in DLE lesions, and more recent work has identified inflammatory fibroblast signatures and collagen-related responses to TGF-β in scarring cutaneous lupus (9,28). These findings support an

interaction between inflammation and fibrosis, although they do not establish that all of these gene-expression changes occur together in the same cells or samples. Epigenetic alterations, including changes in DNA methylation and histone modification, have been implicated in SLE and other autoimmune diseases (33,34). Their specific contribution to persistent fibroblast activation and fibrosis in DLE remains unclear and requires further study.

DISCUSSION

The scarring pattern of discoid lupus erythematosus (DLE) represents a distinct form of tissue damage within the broader spectrum of cutaneous lupus erythematosus (CLE). Unlike subacute CLE (SCLE), which typically resolves without scarring or lasting structural damage, DLE may progress to permanent adnexal destruction and dermal remodelling (13,36). This difference likely reflects the combined effects of immune activation, epithelial injury, and impaired tissue repair.

Scarring DLE lesions are characterizsed by the accumulation of granzyme B–positive cytotoxic T cells at the dermoepidermal junction and around hair follicles. This distribution is consistent with immune-mediated injury to structures involved in tissue regeneration (1,2,16). Sustained type I interferon signalling may further amplify this cytotoxic environment and promote the recruitment of immune mediators, including profibrotic cytokines such as TGF-β and IL-6 (23,26). Together, cytotoxic injury and cytokine signalling may contribute to fibroblast activation and extracellular matrix (ECM) deposition, promoting a fibrotic dermal phenotype over time (27,28).

Changes in the basement membrane zone (BMZ) further distinguish DLE from less destructive CLE variants. These changes include BMZ thickening, duplication of the lamina densa, and abnormalities in anchoring fibrils, which may compromise keratinocyte adhesion and weaken dermoepidermal cohesion (13,35,38,40). Compared with SCLE, BMZ changes in DLE appear more pronounced and have been associated with clinical scarring (35,37). The reported presence of autoantibodies directed against BMZ components also supports a possible autoimmune contribution to ongoing structural injury (43).

Damage to the follicular stem cell compartment may be an important factor in the development of scarring. Immunohistochemical studies have reported depletion of CK15-positive bulge stem cells in areas of dense $CD8^+$ T-cell infiltration in DLE lesions (44,46). Injury to this regenerative niche may impair the restoration of pilosebaceous units and the interfollicular epidermis, thereby favouring a scarring outcome. Disruption of the local immunoregulatory environment that maintains stem cell immune privilege may also contribute to impaired regeneration (51). By contrast, preservation of the bulge region in SCLE is consistent with its typically non-scarring course (44).

At the molecular level, current evidence supports a fibroinflammatory process in DLE. Increased expression of profibrotic genes, including COL1A1, COL3A1, FN1, α-SMA, and TGFB1, points to a tissue environment that may favour sustained matrix accumulation (28,46). Epigenetic changes, including altered DNA methylation and histone regulation, may also influence fibroblast activity; however, their role in maintaining fibroblast activation and limiting regulatory feedback in DLE remains unclear (33,34).

Other factors may contribute to this process. Tissue hypoxia can induce HIF-1α, which may intersect with profibrotic signalling pathways and contribute to collagen synthesis and fibroblast activation (29,49). Oxidative stress associated with chronic inflammation may increase reactive oxygen species (ROS), potentially promoting keratinocyte apoptosis and impairing tissue regeneration (50). These mechanisms may interact with immune-mediated injury and contribute to ongoing fibrotic remodelling.

Clinically, DLE-related damage may present as epidermal thinning, dyspigmentation, and permanent alopecia. Histologically, it may be associated with dermal sclerosis, perifollicular fibrosis, and duplication of the lamina densa. Fibrotic changes may persist or progress after visible inflammation has subsided, suggesting that control of immune activity alone may not be sufficient once tissue remodelling is established.

Overall, the scarring phenotype in DLE appears to arise from interactions among cytotoxic immune injury, BMZ disruption, stem cell damage, and fibroblast activation. This integrated view underscores the importance of studying therapeutic approaches that address both immune dysregulation and fibrotic remodelling, with the aim of preserving regenerative capacity and reducing permanent tissue damage.

This review has several limitations. Relevant studies may have been missed because of language or indexing restrictions, and much of the available evidence comes from small or retrospective studies, which may limit its generalizability. In addition,

understanding of key mechanisms—including BMZ disruption, fibroblast activation, and stem cell dysfunction—remains incomplete, and some explanations are inferred from related conditions rather than supported by direct evidence in CLE.

Declarations

- Funding: The author received no specific funding for this work.
- Ethical approval: Not applicable (this article is a narrative review and does not involve human or animal subjects).

Keywords:

Cutaneous lupus erythematosus, discoid lupus erythematosus, scarring, basement membrane zone, stem cells, fibrosis, TGF-β, granzyme B.

List of Abbreviations

BMZ – Basement membrane zone

CLE – Cutaneous lupus erythematosus

CTL – Cytotoxic T lymphocyte

DLE – Discoid lupus erythematosus

ECM – Extracellular matrix

EMT- Epithelial- to- Mesenchymal Transition.

HIF-1α – Hypoxia-inducible factor 1-alpha

IFN – Interferon

MMP – Matrix metalloproteinase

ROS – Reactive oxygen species

SASP – Senescence-associated secretory phenotype

SCLE – Subacute cutaneous lupus erythematosus

TGF-β – Transforming growth factor beta

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Legends of Tables

Table 1. Key Mechanisms Driving Scarring in Discoid Lupus Erythematosus (DLE)

Key Mechanism	Pathogenic Role
. Immune initiators	- Persistent activation of plasmacytoid dendritic cells → Type I interferons. - $CD8^+$ cytotoxic T lymphocytes release granzyme B, inducing keratinocyte and follicular apoptosis

Profibrotic Mediators	- Transforming Growth Factor-beta (TGF-β) and IL-6 promote fibroblast-to-myofibroblast transition. - Hypoxia (HIF-1α) enhances collagen deposition. - Epigenetic modifications (DNA methylation, histone acetylation) sustain chronic inflammation.
Tissue Remodeling Outcomes	- Basement membrane disruption. - Extracellular matrix (ECM) accumulation. - Loss of hair follicle stem cells → Permanent scarring alopecia
Clinical Impact	- Irreversible scarring and dyspigmentation despite control of active disease. - Significant psychosocial and cosmetic burden

Table 2. Mechanistic Pathways Leading to Scarring in Cutaneous Lupus Erythematosus

Pathogenic Step	**Key Cells**	**Major Mediators**	**Impact on Tissue**
Immune Activation	Plasmacytoid dendritic cells	Type I Interferons	Amplified immune signaling; keratinocyte injury
Cytotoxic Injury	CD8+ T lymphocytes	Granzyme B	Keratinocyte & follicular apoptosis
Macrophage Activation	Macrophages	TGF-β, IL-6	Fibroblast stimulation; collagen synthesis
Fibroblast Transition	Dermal fibroblasts	TGF-β	Myofibroblast formation; ECM deposition
Additional Drivers	Fibroblasts & local tissue	Hypoxia (HIF-1α), Epigenetic changes	Enhanced fibrosis & chronicity
Regenerative Failure	Hair follicle stem cells	Cytotoxic signals	Loss of follicular units; scarring alopecia