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REVIEW ARTICLE

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The pathogenesis of cutaneous lupus erythematosus: The aberrant distribution and function of different cell types in skin lesions

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Abstract

Cutaneous lupus erythematosus (CLE) is an autoimmune disease with a broad range of cutaneous manifestations. In skin lesions of CLE, keratinocytes primarily undergo apoptosis. Interferon-κ(IFN-κ) is belonged to type I interferons (type I IFNs) and is selectively produced by keratinocytes. Recently, keratinocytes selectively produced IFN-κ is identified to be a key to trigger type I interferon responses in CLE. Other immune cells such as plasmacytoid dendritic cells (pDCs) are identified to be relevant origin of type I interferons (type I IFNs) which are central to the development of CLE lesions and responsible for mediating Th1 cell activity. Other types of cells such as neutrophils, B cells and Th17 cells also are involved in the development of this disease. The close interaction of those cells composes a comprehensive and complicated network in CLE. In this review, we discussed the aberrant distribution and function of different cells types involved in this disease and will offer a new direction for research and therapy in the near future.

1 | INTRODUCTION

Lupus erythematosus (LE) is an autoimmune disease with diverse and complicated aetiology, including systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE). CLE is a common manifestation of SLE, resulting in disfiguring scars, permanent hair loss and significant loss of quality of life for patients.[1] According to Gilliam and Sontheimer, CLE can be subdivided into three categories: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE) and chronic cutaneous lupus erythematosus (CCLE).[2] ACLE is often associated with systemic symptoms.[3] Half of SCLE patients meet criteria for SLE, though both of ACLE and SCLE often have mild SLE symptoms.[2] CCLE includes five different forms: discoid LE (DLE), verrucous/hypertrophic LE, LE profundus/panniculitis (LEP), LE tumidus (LET) and chilblain LE (CHLE).[3] DLE is the most

common manifestation of CCLE and DLE rarely presented with systemic manifestations,[4] referring CLE can be an individual disease with only skin involved.[5,6] In fact, clinically CLE traditionally indicates CCLE and SCLE, while ACLE is usually included in SLE.[7] The pathogenesis of CLE is multifactorial and incompletely understood, and involves UV irradiation, smoking, and genetic and sexual factors.[8] Generally, dysfunction of the adaptive and innate immune system in LE results in cytokine and immune complex production, which cause direct tissue injury.[8]

The skin is the primarily affected organ in CLE.[9] Circulating lymphocytes are observed in lesional skin and involved in inflammatory response of skin lesions in CLE.[10-12] Keratinocytes which represent 90% of cells in epidermis are the major target cell in skin and participate in this process.[9] This review is going to discuss abnormal distribution and function of keratinocytes and immune cells in CLE skin lesions, supporting new advances in our understanding of the pathogenesis of CLE.

2 | THE DISTRIBUTION AND ROLE OF KERATINOCYTES IN CLE

The epidermis consists of layers of keratinocytes, and the outer layer of keratinocytes is named stratum corneum which acts as first and outermost physical and chemical barrier against pathogen entry.[13] Keratinocytes consisting in basal layer is the inner epidermic layer, and increased apoptotic keratinocytes are observed in this layer of CLE skin.[14] Keratinocytes are not only the first layer preventing outside stimulus but also the first layer mediating signals to immune cells located in dermis.[13,15,16] Recently, increasing evidence demonstrates keratinocytes playing an important role in the pathogenesis of CLE,[17-19] reminding us of new insight of keratinocytes in this disease.

2.1 | UV-induced apoptosis

Photosensitive is a common characteristic for CLE patients, photosensitivity ranging from 27-100% for SCLE, 25-90% for DLE and 43-71% for LET.[20] UV light consists germicidal UV light (UVC), midrange UV light (UVB) and long-wave UV light (UVA),[21] particularly UVB can induce new skin lesions and exacerbate existing CLE disease.[12]

Keratinocytes account for major cell types in epidermis.[13] UV irradiation can cause skin damage, including keratinocyte apoptosis which is important for initiation, development and perpetuation of CLE and SLE.[11-16] LE patients only with cutaneous lupus erythematosus have slightly higher apoptotic index in both of the lesional skin and non-lesional skin compared with those with systemic manifestation.[14] Different subtypes of CLE have distinct distribution pattern of apoptotic keratinocytes.[22] In DLE, apoptotic keratinocytes locate in basal area of lesional skin, while in SCLE lesions increased apoptotic keratinocytes are observed in super-basal zone.[22]

UV triggers apoptosis in keratinocytes through multiple ways. The nuclear phosphoprotein p53 is a tumour suppressor that associated with apoptosis, and increased p53 expression is observed in keratinocytes after UV irradiation.[23] High level of p53 expression has been found in skin lesions of CLE, and increased p53-positive staining keratinocytes present in the basal layer of the epidermis and follicle.[24] Keratinocytes bear receptor of tumour necrosis factor-α (TNF-α), TNF-α, which is related to cell death and increased in keratinocytes after UV exposure, supporting the notion that TNF-α plays a partial role in mediating UVB-induced apoptosis in keratinocytes.[25] Fas and Fas-ligand (Fas-L)–mediated apoptosis has been implied in the pathogenesis of CLE.[26] It is reported that keratinocytes constitutively express Fas-L and UV irradiation can induce Fas and Fas-L expression; therefore, Fas and Fas-L participate in UV-induced keratinocyte apoptosis.[27] Researchers found significant Fas expression in lesional epidermis of CLE patients, and the Fas expression possibly contributes to higher sensitivity towards apoptosis.[28] Fas-L is expressed in mononuclear cells located around hair follicles in dermal infiltrate while not in epidermic keratinocytes.[26] It is noteworthy that there are more Fas-L–positive cells in DLE skin lesions compared with SLE and SCLE, since DLE is featured by degeneration of hair follicles.[26] These observations may support the idea that Fas-L results in tissue injure.

2.2 | UV-induced pro-inflammatory cytokine production

UV induces keratinocytes to produce tumour necrosis factor-alpha (TNF-α), transforming growth factor-β (TGF-β), interleukin-1α/β (IL-1α/β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10) and interleukin-17 (IL-17).[15,29-32] TNF-α and IL-1 are primary pro-inflammatory cytokines produced in the inflammatory cascade.[21] In SCLE, TNF-α shows high expression in skin lesions and it is predominantly produced by keratinocytes.[33] UV irradiation on keratinocytes results in the production of TNF-α, and subsequently, TNF-α promotes additional inflammatory cytokines in keratinocytes including IL-1.[12] IL-1 can induce intercellular adhesion molecule (ICAM)-1 expression, which is a adhesion molecule supporting leucocyte migration to the skin.[15] IL-1α, one of the members of IL-1, works synergistically with UVB to increase the production of TNF-α, demonstrating that TNF-α can amplify its own effect in an autocrine manner.[34,35] IL-6 is an inflammatory cytokine and is overproduced by monocytes and B cells in serum of SLE patients.[36] With regard to CLE, the upregulation of IL-6 is observed in skin lesions

and keratinocytes is proved to be relevant source of IL-6 production.[19] UV irradiation can induce keratinocytes to release IL-6.[32] Notably, lupus keratinocytes from non-lesional skin produce more IL-6 following Toll-like receptor agonists and UVB stimulation; thus, IL-6 is an important trigger for skin lesions.[19] UV irradiation significantly induces keratinocytes to produce inflammatory chemokines CCL5, CCL20, CCL22 and CXCL8, among which CCL5 and CXCL8 show significantly high expression in CLE; moreover, both of those are mediated by IL-1 and TNF-α.[37] These identifications demonstrate that IL-1 and TNF-α play a significant role in cutaneous immune network.

Impaired or delayed clearance of UV-induced apoptotic keratinocytes is observed in CLE.[38]

Defective clearance results in a release of cell debris along with overflow of endogenous nucleic acid (eNA) which is a ligand for pathogen-recognition receptors (PRRs), resulting in living keratinocytes at dermal-epidermal junction to produce CXCL10 and fuelling the inflammation.[39] In conclusion, these identifications suggest an amplification cycle with the production and release of cytokines that possibly triggered by UV-induced apoptosis.

2.3 | UV-induced autoantibodies

UV irradiation is responsible for autoantigens to re-localize to the surface of apoptotic keratinocytes.[22] Autoantigens presented on surface of keratinocytes are recognized by autoantibodies, resulting in the release of additional cytokines and skin inflammation.[40] Nucleoproteins Ro/SSA and La/SSB can be shifted in blebs and then presented on surface of those cells.[41] Ro52 is an E3 ubiquitin ligase with regulatory role in inflammation. Specific Ro52 autoantibodies can be found in CLE skin lesions and keratinocytes from non-lesional skin of CLE patients show increased Ro52 expression after UV exposure, confirming UV as a triggering factor for skin lesions in patients with Ro52 antibodies.[42] High-mobility group box 1 (HMGB1) is kind of nuclear protein located in nuclei under normal conditions.[43] Increased amounts of HMGB1 expression and translocation were observed in CLE skin lesions, and UV irradiation is able to lead HMGB1 translocation to the cytoplasm.[43] In apoptotic or necrotic keratinocytes, HMGB1 is translocated to the cytoplasm and binds DNA to form immune complex which consequently activates plasmacytoid dendritic cells (pDCs) to produce type I IFNs.[44]

2.4 | Type I interferons and type I IFN-inducible proteins

Type I interferons (type I IFNs) are implicated in the pathogenesis of CLE.[45] Skin lesions of CLE patients have CLE-typical interface dermatitis, and one of its features is type I IFN-inducible chemokine expression, particularly CXCL10.[46] Keratinocytes produce CXCL10 in response to IFN-α, and CXCL10 belongs to CXCR3 ligands.[47] CXCL10 recruits type I helper cells (Th1 cells) to the lesional skin, subsequently initiating the Th1-biased immune activities that may result in keratinocytes necrosis.[47,48] In general, pDCs that infiltrated in skin lesions are identified to be the source of abnormal type I IFNs in CLE.[10] However, there is a lack of systematical evaluation in the origin of IFN in CLE.[17]

IFN-κ included in type I IFNs is selectively expressed by keratinocytes.[49] In CLE, IL-6 is primarily produced by lupus keratinocytes, and enhanced IL-6 response in lupus keratinocytes is mediated by IFN-κ.[19] Recently, Kahlenberg et al [17] have revealed that high level of IFN-κ expression in CLE lesions, and co-expression of IFN-κ and MxA was only seen in epidermis, suggesting epidermic IFN-κ contributes to type I IFN signalling. The abnormal high expression of IFN-κ in lupus keratinocytes prime responsiveness of epithelia to IFN-α and increase keratinocyte photosensitive as well as CD80 expression in pDCs.[17] The utilization of IFN signalling inhibitor baricitinib cancels the above activities, and so does IFN-κ knocked out in keratinocytes.[17] It has been reported that IFN-κ is a genetic risk locus for LE, including some associations with CLE phenotypes.[50] The recent results of IFN-κ in lupus keratinocytes may help to verify the significant role of IFN-κ in the pathogenesis of CLE.

2.5 | Type III interferons

Type III interferons share some commonality with type I interferons, especially in antiviral immunity, while they are different in targeted cells.[51,52] IFN-λ included in type III IFNs is enhanced in epidermis of DLE and SCLE lesions, and it is mainly produced by keratinocytes.[52] Keratinocytes in response to poly(I:C) produce high level of IFN-λ but not IFN-α or IFN-β, indicating type III IFNs is the major IFNs produced by keratinocytes when fight against virus.[52] IFN-λ mainly acts on epithelial cells, and researchers have found that keratinocytes in vitro exposed by IFN-λ1 could produce pro-inflammatory cytokines IL-6, IL-8, CCL3 and CXCL9.[52] CXCL9 expression possibly indicates an early step involved in LE skin disease by supporting the recruitment of pDCs and cytotoxic T cells towards the epidermis, and IFN-λ–related CXCL9 pattern is observed in CLE skin lesions.[52] In turn, accumulated pDCs and cytotoxic T cells produce more IFN-α and IFN-γ to perpetuate the immune response, indicating that the type III IFNs likely cooperate with the type I IFNs in the pathogenesis of CLE.[53]

2.6 | Exosomes derived from keratinocytes

Exosomes are one of the extracellular vesicles (EVs) which harbour proteins, lipid and RNAs, and they can be released by kinds of living cells.[54] Notably, exosomes with miRNA loaded can be transported to target cells for intracellular communication, and keratinocytes are able to release such exosomes in response to environmental stimuli.[55-57] Exosomes isolated from plasma of SLE patients are able to promote PBMC to produce inflammatory cytokines and IFN-α.[58] Recently, Valentina Salvi et al [59] have found that exosomes isolated from the plasma of SLE patients can activate pDCs to produce IFN-α. High level of miR-574 is found in the exosomes derived from plasma of SLE patients, and miR-574 loaded in exosomes can be protected from degradation and effectively reach the endosome of pDCs to initiate this activation.[59] Since skin is the major site of pDC accumulation in CLE, researchers conduct exosomes derived from Hacat (an immortalized human keratinocyte cell line) to verify this interaction, finding out that the exosomes derived from Hacat also enriched in miR-574 and have ability to induce production of IFN-α in pDCs,[59] revealing keratinocytes can regulate cutaneous immunity in CLE through certain exosomes.

3 | THE DISTRIBUTION AND ROLE OF IMMUNE CELLS IN CLE

Cutaneous immune network includes keratinocytes, endothelial cells, dermal DC, T cells and B cells and other immune cells.[15,60] Aberrant distribution of immune cells is commonly found in skin lesions of CLE.[7] It is known that type I IFNs mediated Th1-biased inflammation play a significant role in CLE, pDCs and Th1 cells which are involved in Th1-biased inflammation.[47] A higher quantity of B cell distribution is observed in skin lesions of DLE.[61] Other immune cells such as neutrophils, Th17, Th22 and CTLs also have distribution in skin lesions.[62] It is important to review diverse immune cells in skin lesions in CLE, for it may enlighten us which type of cells plays the predominant role in CLE.

3.1 | Plasmacytoid dendritic cells and type I interferons

Type I IFNs play a significant role in the pathogenesis of CLE.[47] pDCs infiltrate in skin lesions and co-localize with type I IFN-inducible protein MxA, pDCs are identified to be the origin of abnormal type I IFNs in CLE.[10] A case reported that at IFN-α injection site, patients without autoimmune disease show a lupus erythematosus-like histologic reaction in skin.[63] IFN-α induced chemokines such as CXCL9, CXCL10 and CXCL11, all of them are included in CXCR3 ligands and can recruit Th1 cells and CD8 + T cells to the skin.[47] pDCs express CXCR3 and can be recruited to inflamed skin in response to local IFN-α, subsequently fuelling the lesional inflammation by IFN-α production.[37] pDCs express high level of L-selectin, and its ligand PNAd is found in dermal endothelial cells in CLE lesions, indicating recruitment of pDCs to inflammatory sites.[10] Chemerin is a chemoattractant for pDCs, which is found upregulation in skin lesions of lupus patients.[64] In murine model, UVB irradiation induces pDC infiltration and activation in sun-exposure skin, simultaneously elevated chemerin is also observed in the same site, and chemerin expression positively correlates with pDC accumulation.[64] More significantly, vulnerable to UVB irradiation, LE-prone MRL/lpr mouse have dramatically accumulation of pDCs and chemerin,[64] probably indicating the photosensitivity of LE patients.

3.2 | Neutrophils and IFN-α induction

Neutrophils can form neutrophil extracellular traps (NETs) in response to microbial invasion, and neutrophils are associated with autoimmune disease by self-nucleic acid production.[65] Accumulated NETs are observed in dermal-epidermal junction of skin lesions in different subtypes of cutaneous lupus erythematosus.[11] Notably, characterized by tissue damage and scarring, DLE shows more NETs than SCLE which without scarring.[65] NETs consist of chromatin fibres and associated bactericidal proteins.[62] In lesional skin of CLE, an antimicrobial peptide LL-37 is observed.[66] LL-37 is produced by keratinocytes while senses danger signals and LL-37 is associated with NETs by converting self-nucleic acids molecular to TLR7/9 ligands, subsequently activate pDCs to produce type I IFNs.[11,13] Similarly, in lesional skin of psoriasis, anionic self-DNA is found complexed to LL-37, and the LL-37⁄self-DNA complex is able to trigger TLR9-mediated type I IFN production in pDCs.[67] Moreover, LL-37 contributes to DNA-mediated activation of keratinocytes.[68] LL-37 co-express with MxA in skin lesions of CLE patients, and keratinocytes have significant enhanced CLE-associated cytokine production when eNA stimulation is combined with LL-37, suggesting LL-37 is more than immunostimulatory on its own.[39]

3.3 | Th1, Th2 cells and IFN-γ

Decreased Th1 cells are observed in serum of CLE patients, demonstrating skin-targeted migration of Th1

cells.[47] It has been demonstrated that Th1 cells participate in the inflammation promoted by IFN-α.[69] Since IFN-α results in CXCL10 production in keratinocytes, CXCL10 as ligand for CXCR3 receptor is characteristic for Th1 cells, leading Th1 cells towards lesional skin.[37,69] Th1 cells also produce IFN-γ. In one hand, IFN-γ contributes to skin lesion formation by mediating the downstream inflammatory effects, and in another hand, IFN-γ amplifies CXCL9, CXCL10 and CXCL11 production.[70] Moreover, IFN-γ enhances T lymphocyte-keratinocyte adhesion by inducing keratinocytes to produce intracellular adhesion molecule 1(ICAM-1).[71] CXCL10 could also be recognized by Th2 cells.[72] The notion that predominance of Th1 over Th2 has been generally accepted in CLE.[7] CCR5 and CCR3 represent Th1 cell and Th2 cell, respectively, and there is a higher CCR5 and lower CCR3 expression rate in circulating CD4 lymphocytes in CLE, which indicates an enhanced Th1-to-Th2 ratio in peripheral lymphocytes of patients with widespread active CLE skin lesions.[69] The importance of Th2 cells in CLE still needs further investigations.

3.4 | Th17 cells

The contribution of Th17 cells in CLE pathogenesis remains to be determined. In DLE, IL-17A, which is produced by Th17 cells, has high level in serum, while in SCLE the elevated level of IL-17A is not found.[73] Tanasescu et al [73] have found that serum of the IL-17A level correlates positively with the number of IL-17 + lymphocytes in the cutaneous inflammatory infiltrate in DLE, suggesting that an important IL-17A source is IL-17A + lymphocytes from the skin. Lupus keratinocytes have enhanced ability to produce IL-6, and it has been implied that Th17 cell activities are mediated by IL-6.[19,74] Although IL-6 immune staining and IL-17A immune staining are observed in majority of CLE cases, there is no close correlation observed between them.[75] On the contrary, IL-17A presents IFN-α–related expression pattern in skin lesions of CLE patients.[75] Since type I interferons are well-known in contribution to CLE, we are likely to confirm Th17 cells have a pathogenic role in CLE. However, another study revealed the absence of Th17 cells in DLE skin lesions.[76] More recently, a hospital-based case-control study investigated that ratio of Aryl hydrocarbon receptor (AhR), which is associated with autoimmune disease,[77-79] is significantly high in Th17 cells of SLE patients; moreover, the ratio of AhR is positively correlated with skin lesions, and these results demonstrated that AhR ratio may be a promising marker to indicate skin lesion development in SLE.[80] Altogether, the exact effect of Th17 cells in CLE is still controversial.

3.5 | B cells

It has been implied that B cells participate in CLE not only by antigen-presenting but also by autoantibodies and cytokine production.[81] A higher quantity of B cells is found in both circulation and skin lesions in DLE.[61,82] Moreover, enhanced B cell infiltration presents as skin lesions progress from the early phase without dermal scarring to the later phase with dermal scarring, indicating that B cells become a greater component of the inflammatory cell infiltrate in later DLE lesions.[83] B cell–activating factor (BAFF) is associated with survival and homeostasis activities of B cells.[84] Recently, researchers have demonstrated the upregulation of BAFF in skin lesions of active CLE patients, and BAFF was particularly expressed by keratinocytes in the lower epidermal layer in areas with the strongest inflammatory infiltrate, keratinocytes under immunostimulatory DNA motif stimulation can produce BAFF.[85] All of BAFF receptors (BAFF-R, BCMA and TACI) are only found in lymphoid cells, not in keratinocytes,[85] adding to the importance of the interaction between keratinocytes and B cells or other lymphocytes in CLE-typical interface dermatitis.

3.6 | Cytotoxic CD8 + T cells

Cytotoxic CD8 + T cells (CTLs) participate in inflammatory infiltrate in CLE lesions,[47,61] as it is proved by decreased CXCR5 + CD8+ T cells in the circulation of CLE patients.[47,82] Some studies even reported that CD8 + T cells to be the predominant T cells in DLE skin lesions.[46,86] In dermal-epidermal junction of the CLE lesions, CTLs that express granzyme B are observed, and granzyme B has ability to mediate apoptosis.[87] Generally, CTLs present in CLE lesions and support CLE lesions through apoptosis-mediated molecules production. Still, the importance of CTLs in CLE needs further elucidation.

3.7 | Other immune cells

Regulatory T cells (Treg) are responsible for immune suppresses, and Treg cells play an important role in allergies and autoimmune disease,[88] and depletion of those cells is observed in some autoimmune disease.[89,90] In skin lesions of CLE patients, it has been reported that reduced Foxp3 + Treg cells were found and restrict to inflammation site; however, there is no correlation between Treg cell frequency and different subtypes of CLE.[91] Attention on Th22 cells was arising for IL-22 production,[92,93] IL-22 is a cytokine produced by Th1, Th17 cells and innate lymphoid cells (ILCs), and IL-22 mainly affects keratinocyte activities in skin, including keratinocyte proliferation and epidermal hyperplasia, inhibits terminal

differentiation of keratinocytes and promotes the production of antimicrobial proteins.[93] IL-22 highly expresses in skin lesions of psoriasis patients, and it is identified to be major origin of abnormal IL-22 production.[94-96] In skin lesions of DLE patients, researchers found significantly high Th22 percentage, and it is interesting that higher Th22 percentage indicates lower Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score; thus, IL-22 might be a good indicator for tissue repair more than in inflammation.[97]

4 | PREVENTION AND THERAPY

4.1 | Prevention

UV light is the most important external risk of CLE and usage of sunscreen can reduce type I/III IFNs and IFN-inducible protein production, thus alleviating typical IFN-driven inflammatory response in CLE patients.[98] It is critical for LE patients to avoid long time and over-dosage of sun exposure. Vitamin D reduction may occur in LE patients due to sun avoidance; thus, it is advisable for LE patients to supplement vitamin D.[99] Smoking is another risk of CLE which can fuel CLE disease activity by promoting pro-inflammatory cytokine activities.[100] It is quite necessary for patients to reduce and drop smoking, developing a healthy lifestyle. Certain type of drugs may be also selected carefully, for inducing skin lesions, which is drug-induced cutaneous lupus erythematosus (DI-CLE). In a recent study, present ratio of DI-CLE in 232 patients is 29%.[101] A retrospective chart review reveals that 88 cases developed to DI-SCLE in Denmark, and in this review, proton-pump inhibitors, antihypertensives and antifungals are suggested to be the most common drugs; therefore, it might be important for dermatologist to recognize and use these drugs which are associated with 'lupus-precipitating'.[102]

4.2 | Established therapies

Antimalarials are still the first-line systemic therapy for CLE, and quinacrine, chloroquine and hydroxychloroquine are the three currently used antimalarials.[103] In skin lesion treatment of lupus spectrum diseases, the combination of hydroxychloroquine (HCQ) and chloroquine (CQ) at a dosage of 100mg/day is identified to be safe and quite effective.[104] HCQ shows higher overall efficacy compared with CQ, which is reported by a systematic review and meta-analysis.[105] HCQ is superior to CQ with its greater risk of toxic retinopathy.[106] HCQ is the preferred agent because of its efficacy and tolerability.[4,107] Considering the safety, HCQ can be also prescribed to pregnant women.[108] In a double-blinded randomized trial among 103 CLE patients in Japan, global assessment reveals greater improvements in the HCQ group compared with placebo group (51.4% vs 8.7%).[107] HCQ adds its effect by accumulating in lysosomes and increasing the pH in lysosomes to interfere the immune response.[108] It has been reported that HCQ significantly inhibits pDC response to TLR9 but not to TLR7 and TLR8 to produce IFN-α.[109-111] HCQ could inhibit the pro-inflammatory cytokines IL-6, IL-α, IL-1β and TNF-α and blocks T cell activation by disrupting the T cell receptor–dependent calcium signalling.[112] Recently, HCQ is reported to significantly inhibit S100 proteins and S100 proteins which are ligands for TLR4 are related to organ involvement in SLE. HCQ reduces S100 proteins and then results in inhibition of TLR4 signalling, which may indicate the mechanism of skin lesion alleviation in SLE patients.[113] Also, in a more recently case reported HCQ treatment in a 34-year-old woman with DLE, and after 5 months of HCQ administration at a dose of 200 mg/day without prednisolone (PSL) dosage increased, the skin lesions completely resolved.[114] Topical corticosteroids are the first-line topical therapy for skin lesions in CLE, while corticosteroids can result in skin atrophy in CLE treatment.[115] Tacrolimus, a topical calcineurin inhibitor, achieved great improvement in hyperkeratotic lesions of CCLE without major side effects.[115] Topical calcineurin inhibitors could be a better alternative for corticosteroids.

Methotrexate, which is implied in rheumatoid arthritis and other autoimmunity disease, is considered as second-line treatment for CLE.[67] It has been implied that methotrexate (MTX) suppresses ICAM-1 to inhibit migration of lymphocytes to skin in psoriatic.[116] Low dosage of MTX that applied in LE patients demonstrates significant decrease in disease activities as well as improvement of skin lesions.[117] Low dosage of MTX is quite effective in curing skin lesions in CLE patients, especially in those who are not response to standard therapeutic regimens.[118] Other cases indicate MTX is effective for a 30-year-old female patient with severe SCLE refractory to therapy with antimalarials and corticosteroids, and after 4 months of MTX treatment at a dosage of 25mg/week, skin lesions completely cleared.[119] However, side effects of MTX are also observed and are quickly resolved when MTX is suspended.[117,119] Therefore, MTX should be selected carefully and monitored closely for adverse reactions.

4.3 | Targeted therapies

In a recent clinical trial in SLE patients, IIB059, a monoclonal antibody, binds to blood DC antigen 2 to inhibit production of type I IFNs, adding its effect on pDC activity. Administration of IIB059 in SLE patients especially those with cutaneous manifestations achieves significant improvement of immune infiltrates in skin lesions, and CLASI score decreases.[120] B cell–depleting therapy, rituximab, is applied in treating SLE.[85] Rituximab presents effectiveness in certain

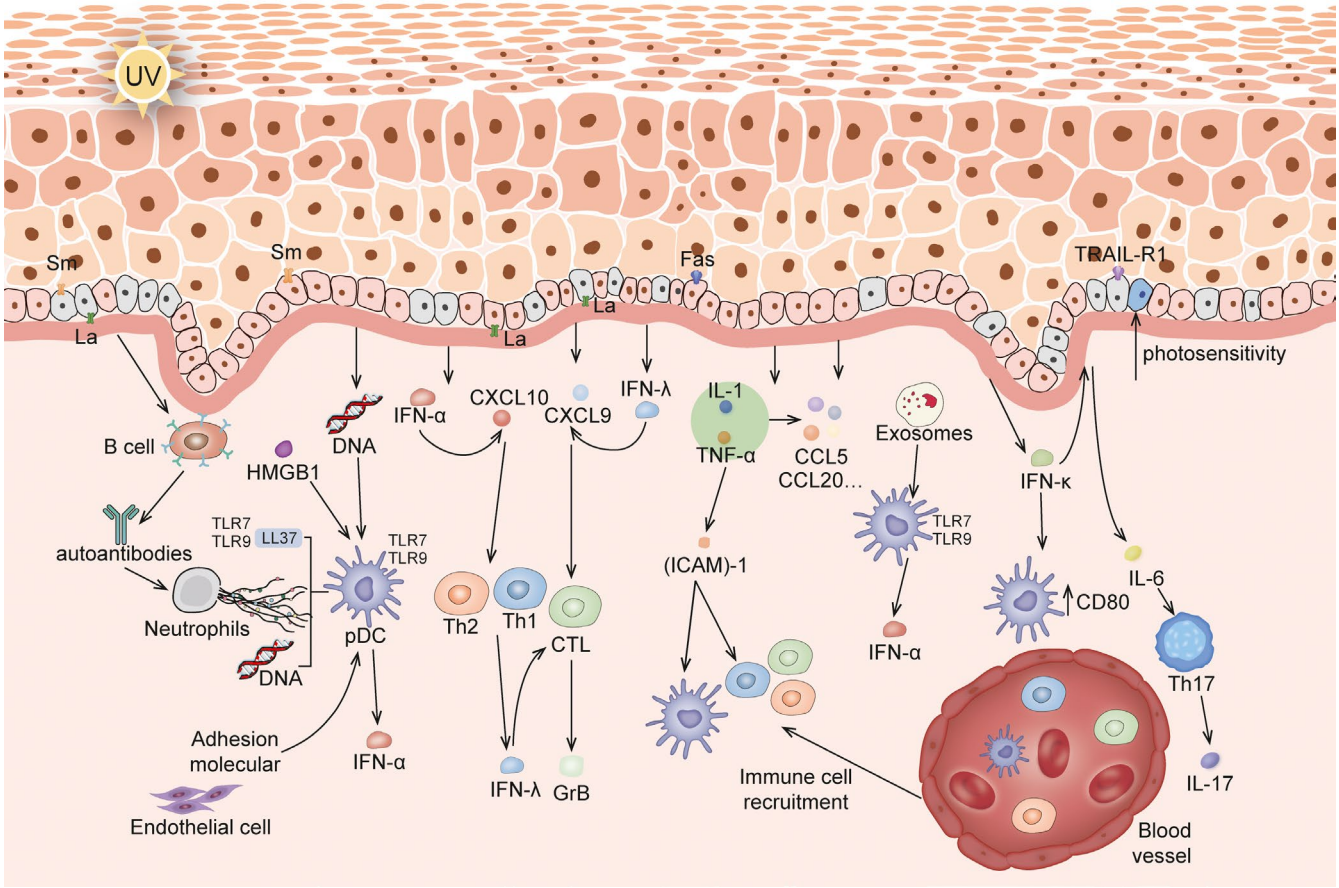

FIGURE 1 Different immune cell types compose the complex network in CLE and perpetuate the lesion formation. Keratinocytes produce pro-inflammatory cytokines in response to UV irradiation or other stimulation. These pro-inflammatory cytokines are able to recruit pDCs, other immune cells. Endogenous DNA released by apoptotic keratinocytes and NETs amplify the production of IFN-α in pDCs. Keratinocytes released exosomes also contribute to this progress. IFN-α involved in type I IFNs induces the recruitment of Th1 cells to skin and induces Th1 cells to produce IFN-γ. IFN-κ produced by keratinocyte prime type I IFN response and increase photosensitivity, and IFN-κ can regulate IL-6, through that way may contribute to IL-17 production by Th17 cells. UV, ultraviolet; pDCs, plasmacytoid dendritic cells; IFN, interferon; NETs, neutrophil extracellular traps

types of CLE, particularly in ACLE, SCLE or non-specific cutaneous lesions.[121] Although in CCLE cases, Vital et al [122] have observed that rituximab presents no effects, and some patients even experience flares in cutaneous disease. These identifications reveal that B cells possibly play a different role in CLE subtypes and provoke a question how B cells participate in the pathogenesis of CLE. Belimumab is a monoclonal antibody against BAFF (B cell–activating factor) to inhibit B cell activation. Belimumab is applied for SLE treatment by the FDA; moreover, it presents great effect in skin lesion treatment of SLE patients.[123]

Sifalimumab is an anti-IFN-α monoclonal antibody, in a phase IIb study of sifalimumab in SLE patients, and it shows only a reserved improvement in cutaneous lupus scores.[124] IFN-γ plays a pathogenic role in CLE, and a phase I clinical trial is conducted to evaluate clinical efficacy of AMG 811, which is an anti-IFN-γ antibody, in DLE patients. Unfortunately, AMG 811 adds no significant improvement in this clinical trial.[125] Since there are increasing findings showing the discrepancy in lupus trials, Jasmine N. et al [19] held the idea that IFN-κ plays an important role in CLE and perhaps the source of interferon in the skin (pDC/IFN-α vs. keratinocyte/IFN-κ) may predict which drug will yield a better response, in contrast to sifalimumab with only IFN-α blockade.[124,126] Anifrolumab blocks type I IFN receptor, consequently leading both of IFN-α blockade and IFN-κ blockade, achieving significant clinical improvement.[127] Tocilizumab, an anti-IL-6 receptor antibody, achieves improvement in decreasing systemic activities as well as cutaneous manifestation.[128,129] However, there is a study that shows no clinical improvement in CLE with IL-6 blockade.[130] The potential therapeutic role of IL-6 blockade in the treatment of CLE remains unclear. In a trial, an anti–IL-10 monoclonal antibody decreased cutaneous lesions, joint symptoms and SLEDAI scores of SLE subjects.[131] Ustekinumab is a monoantibody for IL-12 and IL-23,[132] and several cases report ustekinumab is effective in treating cutaneous

manifestation.[132-135] Spleen tyrosine kinase (SYK) is a protein kinase involved in cell proliferation and regulation of inflammatory pathways, and significant expression of phosphorylated SYK (pSYK) is observed in keratinocytes of CLE skin.[136] GSK143, a SYK inhibitor, is utilized in keratinocytes with synthetic immunostimulatory nucleic acid poly(I:C) and poly(dA:dT) stimulation, and GSK143 significantly inhibits keratinocytes to produce pro-inflammatory cytokines that are induced by type I IFNs,[136] indicating that pSYK may be a promising drug target for CLE treatment. Accordingly, phase I clinical trial of SYK inhibitor (GSK2646264) in CLE is now carrying on, and an oral SYK inhibitor lanraplenib (GS-9876) is being tested in parallel with filgotinib in a phase II study in female patients with moderate-to-severe CLE.[137]

5 | CONCLUSIONS

CLE usually presents as one of the manifestations of SLE patients; however, there are also a proportion of SLE patients present without cutaneous manifestations.[3] About 18% of CLE patients in a study are reported to progress to SLE during observation period.[138] While there are still some CLE cases never develop to SLE, indicating there is no clear line between these two entities and they preserve some differences in the pathogenesis of skin damage.[3]

A set of distinct differences are presented between ACLE (CLE-associated SLE) and DLE (the most common of CCLE and rarely progress to SLE) in clinical features, histopathology and serologic autoantibodies.[7] Skin-deposited IgG is a critical pathologic factor in the development of skin damage in SLE.[139] With regard to CLE, skin lesions present as interface dermatitis which is dominated by type I and III interferons regulated pro-inflammatory cytokines.[137] It is now believed that CLE without systemic manifestations likely to be an individual disease and it is important to revolutionize our understanding of the pathological mechanisms underlying this disease. The following factors are required for the development of CLE: (a) UV irradiation induces keratinocyte apoptosis and altered cytokine release; (b) autoantibodies bind to autoantigens located in apoptotic keratinocytes; (c) and recruitment of lymphocytes to perpetuate the cutaneous immune response (Figure 1).

There are raising evidences that keratinocytes are not just apoptotic cells in CLE, and therapy that mainly target IFN-κ receives significant clinical improvement. In conclusion, these observations may enlighten us a new direction for CLE research.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

Xinyu Zhou conducted the literature review and wrote the main manuscript. Jinli Yan served as content advisor for the manuscript. Qianjin Lu and Honghao Zhou assisted with the literature review. Lan Fan served as primary content decision-maker. All authors have read and approved the final manuscript.

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REFERENCES

1. Klein R, Moghadam-Kia S, Taylor L, et al. Quality of life in cutaneous lupus erythematosus. *J Am Acad Dermatol*. 2011;64(5):849–858. http://dx.doi.org/10.1016/j.jaad.2010.02.008
2. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. *J Am Acad Dermatol*. 1981;4(4):471–475. http://dx.doi.org/10.1016/s0190-9622(81)80261-7
3. Werth VP. Clinical manifestations of cutaneous lupus erythematosus. *Autoimmun Rev*. 2005;4(5):296–302. http://dx.doi.org/10.1016/j.autrev.2005.01.003
4. Walling HW, Sontheimer RD. Cutaneous Lupus Erythematosus. *Am J Clin Dermatol*. 2009;10(6):365–381. http://dx.doi.org/10.2165/11310780-000000000-00000
5. Berthier CC, Tsoi LC, Reed TJ, et al. Molecular Profiling of Cutaneous Lupus Lesions Identifies Subgroups Distinct from Clinical Phenotypes. *J Clin Med*. 2019;8(8):1244. http://dx.doi.org/10.3390/jcm8081244
6. Filotico R, Mastrandrea V. Cutaneous lupus erythematosus: clinico-pathologic correlation. *G Ital Dermatol Venereol*. 2018;153(2):216-229. https://www.ncbi.nlm.nih.gov/pubmed/29368845
7. Li Q, Wu H, Liao W, et al. A comprehensive review of immune-mediated dermatopathology in systemic lupus erythematosus. *J Autoimmun*. 2018;93:1–15. http://dx.doi.org/10.1016/j.jaut.2018.07.007
8. Blake SC, Daniel BS. Cutaneous lupus erythematosus: A review of the literature. *Int J Womens Dermatol*. 2019;5(5):320–329. http://dx.doi.org/10.1016/j.ijwd.2019.07.004
9. Zhang Y, Wu J, Han Y, Shi Z, Wang L. Pathogenesis of cutaneous lupus erythema associated with and without systemic lupus erythema. *Autoimmun Rev*. 2017;16(7):735–742. http://dx.doi.org/10.1016/j.autrev.2017.05.009
10. Farkas L, Beiske K, Lund-Johansen F, Brandtzaeg P, Jahnsen FL. Plasmacytoid Dendritic Cells (Natural Interferon- α/β-Producing Cells) Accumulate in Cutaneous Lupus Erythematosus Lesions. *Am J Pathol*. 2001;159(1):237–243. http://dx.doi.org/10.1016/s0002-9440(10)61689-6
11. Villanueva E, Yalavarthi S, Berthier CC, et al. Netting Neutrophils Induce Endothelial Damage, Infiltrate Tissues,

and Expose Immunostimulatory Molecules in Systemic Lupus Erythematosus. *J Immunol*. 2011;187(1):538–552. http://dx.doi.org/10.4049/jimmunol.1100450

12. Robinson ES, Werth VP. The role of cytokines in the pathogenesis of cutaneous lupus erythematosus. *Cytokine*. 2015;73(2):326–334. http://dx.doi.org/10.1016/j.cyto.2015.01.031
13. Klicznik MM, Szenes-Nagy AB, Campbell DJ, Gratz IK. Taking the lead – how keratinocytes orchestrate skin T cell immunity. *Immunol Lett*. 2018;200:43–51. http://dx.doi.org/10.1016/j.imlet.2018.06.009
14. Skiljevic D, Bonaci-Nikolic B, Brasanac D, Nikolic M. Apoptosis of keratinocytes and serum DNase I activity in patients with cutaneous lupus erythematosus: relationship with clinical and immunoserological parameters. *J Eur Acad Dermatol Venereol*. 2017;31(3):523–529. http://dx.doi.org/10.1111/jdv.13943
15. Matejuk A. Skin Immunity. *Arch Immunol Ther Exp (Warsz)*. 2018;66(1):45–54. http://dx.doi.org/10.1007/s00005-017-0477-3
16. Nestle FO, Di Meglio P, Qin J-Z, Nickoloff BJ. Skin immune sentinels in health and disease. *Nat Rev Immunol*. 2009;9(10):679–691. http://dx.doi.org/10.1038/nri2622
17. Sarkar MK, Hile GA, Tsoi LC, et al. Photosensitivity and type I IFN responses in cutaneous lupus are driven by epidermal-derived interferon kappa. *Ann Rheum Dis*. 2018;77(11):1653–1664. http://dx.doi.org/10.1136/annrheumdis-2018-213197
18. Tsoi LC, Hile GA, Berthier CC, et al. Hypersensitive IFN Responses in Lupus Keratinocytes Reveal Key Mechanistic Determinants in Cutaneous Lupus. *J Immunol*. 2019;202(7):2121–2130. http://dx.doi.org/10.4049/jimmunol.1800650
19. Stannard JN, Reed TJ, Myers E, et al. Lupus Skin Is Primed for IL-6 Inflammatory Responses through a Keratinocyte-Mediated Autocrine Type I Interferon Loop. *J Invest Dermatol*. 2017;137(1):115–122. http://dx.doi.org/10.1016/j.jid.2016.09.008
20. Kim A, Chong BF. Photosensitivity in cutaneous lupus erythematosus. *Photodermatol Photoimmunol Photomed*. 2013;29(1):4–11. http://dx.doi.org/10.1111/phpp.12018
21. Lin JH, Dutz JP, Sontheimer RD, Werth VP. Pathophysiology of Cutaneous Lupus Erythematosus. *Clin Rev Allergy Immunol*. 2007;33(1-2):85–106. http://dx.doi.org/10.1007/s12016-007-0031-x
22. Norris DA, Whang K, David-Bajar K, Bennion SD. The Influence of Ultraviolet Light on Immunological Cytotoxicity in the Skin. *Photochem Photobiol*. 1997;65(4):636–646. http://dx.doi.org/10.1111/j.1751-1097.1997.tb01905.x
23. Cotton J, Spandau DF. Ultraviolet B-radiation dose influences the induction of apoptosis and p53 in human keratinocytes. *Radiat Res*. 1997;147(2):148-55.
24. Chung JH, Kwon OS, Eun HC, et al. Apoptosis in the Pathogenesis of Cutaneous Lupus Erythematosus. *Am J Dermatopathol*. 1998;20(3):233–241. http://dx.doi.org/10.1097/00000372-199806000-00002
25. Schwarz A, Bhardwaj R, Aragane Y, et al. Ultraviolet-B-Induced Apoptosis of Keratinocytes: Evidence for Partial Involvement of Tumor Necrosis Factor-α in the Formation of Sunburn Cells. *J Invest Dermatol*. 1995;104(6):922–927. http://dx.doi.org/10.1111/1523-1747.ep12606202
26. Baima B, Sticherling M. Apoptosis in different cutaneous manifestations of lupus erythematosus. *Br J Dermatol*. 2001;144(5):958–966. http://dx.doi.org/10.1046/j.1365-2133.2001.04182.x
27. Leverkus M, Yaar M, Gilchrest BA. Fas/Fas Ligand Interaction Contributes to UV-Induced Apoptosis in Human Keratinocytes. *Exp Cell Res*. 1997;232(2):255–262. http://dx.doi.org/10.1006/excr.1997.3514
28. Toberer F, Sykora J, Göttel D, et al. Apoptotic signal molecules in skin biopsies of cutaneous lupus erythematosus: analysis using tissue microarray. *Exp Dermatol*. 2013;22(10):656–659. http://dx.doi.org/10.1111/exd.12216
29. Köck A, Schwarz T, Kirnbauer R, et al. Human keratinocytes are a source for tumor necrosis factor alpha: evidence for synthesis and release upon stimulation with endotoxin or ultraviolet light.. *J Exp Med*. 1990;172(6):1609–1614. http://dx.doi.org/10.1084/jem.172.6.1609
30. Takashima A, Bergstresser PR. Impact of UVB Radiation on the Epidermal Cytokine Network. *Photochem Photobiol*. 1996;63(4):397–400. http://dx.doi.org/10.1111/j.1751-1097.1996.tb03054.x
31. Kuhn A, Sontheimer RD. Cutaneous lupus erythematosus: molecular and cellular basis of clinical findings. *Curr Dir Autoimmun*. 2008;10:119–14. https://www.ncbi.nlm.nih.gov/pubmed/18460883
32. Wozniacka A, Lesiak A, Boncela J, Smolarczyk K, McCauliffe DP, Sysa-Jedrzejowska A. The influence of antimalarial treatment on IL-1β, IL-6 and TNF-α mRNA expression on UVB-irradiated skin in systemic lupus erythematosus. *Br J Dermatol*. 2008;159(5):1124–30. http://dx.doi.org/10.1111/j.1365-2133.2008.08804.x
33. Zampieri S, Alaibac M, Iaccarino L, et al. Tumour necrosis factor is expressed in refractory skin lesions from patients with subacute cutaneous lupus erythematosus. *Ann Rheum Dis*. 2006;65(4):545–548. http://dx.doi.org/10.1136/ard.2005.039362
34. Werth VP, Zhang W, Dortzbach K, Sullivan K. Association of a Promoter Polymorphism of Tumor Necrosis Factor-α with Subacute Cutaneous Lupus Erythematosus and Distinct Photoregulation of Transcription. *J Invest Dermatol*. 2000;115(4):726–730. http://dx.doi.org/10.1046/j.1523-1747.2000.00118.x
35. Bashir MM, Sharma MR, Werth VP. UVB and Proinflammatory Cytokines Synergistically Activate TNF-α Production in Keratinocytes through Enhanced Gene Transcription. *J Invest Dermatol*. 2009;129(4):994–1001. http://dx.doi.org/10.1038/jid.2008.332
36. Mellor-Pita S, Citores MJ, Castejon R, et al. Monocytes and T lymphocytes contribute to a predominance of interleukin 6 and interleukin 10 in systemic lupus erythematosus. *Cytometry B Clin Cytom*. 2009;76B(4):261–270. http://dx.doi.org/10.1002/cyto.b.20468
37. Meller S, Winterberg F, Gilliet M, et al. Ultraviolet radiation-induced injury, chemokines, and leukocyte recruitment: An amplification cycle triggering cutaneous lupus erythematosus. *Arthritis Rheum*. 2005;52(5):1504–1516. http://dx.doi.org/10.1002/art.21034
38. Kuhn A, Herrmann M, Kleber S, et al. Accumulation of apoptotic cells in the epidermis of patients with cutaneous lupus erythematosus after ultraviolet irradiation. *Arthritis Rheum*. 2006;54(3):939–950. http://dx.doi.org/10.1002/art.21658
39. Scholtissek B, Zahn S, Maier J, et al. Immunostimulatory Endogenous Nucleic Acids Drive the Lesional Inflammation in Cutaneous Lupus Erythematosus. *J Invest Dermatol*. 2017;137(7):1484–1492. http://dx.doi.org/10.1016/j.jid.2017.03.018
40. Caricchio R, McPhie L, Cohen PL. Ultraviolet B Radiation-Induced Cell Death: Critical Role of Ultraviolet Dose in Inflammation and Lupus Autoantigen Redistribution. *J Immunol*. 2003;171(11):5778–5786. http://dx.doi.org/10.4049/jimmunol.171.11.5778

41. Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes.. *J Exp Med*. 1994;179(4):1317–1330. http://dx.doi.org/10.1084/jem.179.4.1317
42. Oke V, Vassilaki I, Espinosa A, et al. High Ro52 Expression in Spontaneous and UV-Induced Cutaneous Inflammation. *J Invest Dermatol*. 2009;129(8):2000–2010. http://dx.doi.org/10.1038/jid.2008.453
43. Barkauskaite V, Ek M, Popovic K, Harris HE, Wahren-Herlenius M, Nyberg F. Translocation of the novel cytokine HMGB1 to the cytoplasm and extracellular space coincides with the peak of clinical activity in experimentally UV-induced lesions of cutaneous lupus erythematosus. *Lupus*. 2007;16(10):794–802. http://dx.doi.org/10.1177/0961203307081895
44. Abdulahad DA, Westra J., Limburg PC, Kallenberg CGM, Bijl M. HMGB1 in systemic lupus Erythematosus: Its role in cutaneous lesions development. *Autoimmun Rev*. 2010;9(10):661–665. http://dx.doi.org/10.1016/j.autrev.2010.05.015
45. Braunstein I, Klein R, Okawa J, Werth VP. The interferon-regulated gene signature is elevated in subacute cutaneous lupus erythematosus and discoid lupus erythematosus and correlates with the cutaneous lupus area and severity index score. *Br J Dermatol*. 2012;166(5):971–975. http://dx.doi.org/10.1111/j.1365-2133.2012.10825.x
46. Wenzel J, Zahn S, Mikus S, Wiechert A, Bieber T, Tüting T. The expression pattern of interferon-inducible proteins reflects the characteristic histological distribution of infiltrating immune cells in different cutaneous lupus erythematosus subsets. *Br J Dermatol*. 2007;157(4):752–757. http://dx.doi.org/10.1111/j.1365-2133.2007.08137.x
47. Wenzel J, Wörenkämper E, Freutel S,et al. Enhanced type I interferon signalling promotes Th1-biased inflammation in cutaneous lupus erythematosus. *J Pathol*. 2005;205(4):435–442. http://dx.doi.org/10.1002/path.1721
48. Lauffer F, Jargosch M, Krause L, et al. Type I Immune Response Induces Keratinocyte Necroptosis and Is Associated with Interface Dermatitis. *J Invest Dermatol*. 2018;138(8):1785–1794. http://dx.doi.org/10.1016/j.jid.2018.02.034
49. LaFleur DW, Nardelli B, Tsareva T, et al. Interferon-κ, a Novel Type I Interferon Expressed in Human Keratinocytes. *J Biol Chem*. 2001;276(43):39765–39771. http://dx.doi.org/10.1074/jbc.m102502200
50. Harley ITW, Niewold TB, Stormont RM, et al. The Role of Genetic Variation Near Interferon-Kappa in Systemic Lupus Erythematosus. *J Biomed Biotechnol*. 2010;2010:1–11. http://dx.doi.org/10.1155/2010/706825
51. Chyuan I-T, Tzeng H-T, Chen J-Y. Signaling Pathways of Type I and Type III Interferons and Targeted Therapies in Systemic Lupus Erythematosus. *Cells*. 2019;8(9):963. http://dx.doi.org/10.3390/cells8090963
52. Zahn S, Rehkämper C, Kümmerer BM et al. Evidence for a Pathophysiological Role of Keratinocyte-Derived Type III Interferon (IFNλ) in Cutaneous Lupus Erythematosus. *J Invest Dermatol*. 2011;131(1):133–140. http://dx.doi.org/10.1038/jid.2010.244
53. Yoneyama H, Matsuno K, Zhang Y, et al. Evidence for recruitment of plasmacytoid dendritic cell precursors to inflamed lymph nodes through high endothelial venules. *Int Immunol*. 2004;16(7):915–928. http://dx.doi.org/10.1093/intimm/dxh093
54. Simons M, Raposo G. Exosomes – vesicular carriers for intercellular communication. *Curr Opin Cell Biol*. 2009;21(4):575–581. http://dx.doi.org/10.1016/j.ceb.2009.03.007
55. Cicero AL, Delevoye C, Gilles-Marsens F, et al. Exosomes released by keratinocytes modulate melanocyte pigmentation. *Communications*. 2015;6(1):7506. http://dx.doi.org/10.1038/ncomms8506
56. Kotzerke K, Mempel M, Aung T, et al. Immunostimulatory activity of murine keratinocyte-derived exosomes. *Exp Dermatol*. 2013;22(10):650–655. http://dx.doi.org/10.1111/exd.12230
57. Liu Y, Xue L, Gao H, et al. Exosomal miRNA derived from keratinocytes regulates pigmentation in melanocytes. *J Dermatol Sci*. 2019;93(3):159–167. http://dx.doi.org/10.1016/j.jdermsci.2019.02.001
58. Lee JY, Park JK, Lee EY, Lee EB, Song YW. Circulating exosomes from patients with systemic lupus erythematosus induce a proinflammatory immune response. *Arthritis Res Ther*. 2016;18(1):264. http://dx.doi.org/10.1186/s13075-016-1159-y
59. Salvi V, Gianello V, Busatto S, et al. Exosome-delivered microRNAs promote IFN-α secretion by human plasmacytoid DCs via TLR7. *JCI Insight*. 2018;3(10):e98204. http://dx.doi.org/10.1172/jci.insight.98204
60. Eyerich S, Eyerich K, Traidl-Hoffmann C, Biedermann T. Cutaneous Barriers and Skin Immunity: Differentiating A Connected Network. *Trends Immunol*. 2018;39(4):315–327. http://dx.doi.org/10.1016/j.it.2018.02.004
61. Xie Y, Jinnin M, Zhang X, et al. Immunohistochemical characterization of the cellular infiltrate in discoid lupus erythematosus. *Biosci Trends*. 2011;5(2):83–88. http://dx.doi.org/10.5582/bst.2011.v5.2.83
62. Achtman JC, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Arthritis Res Ther*. 2015;17(1):182. http://dx.doi.org/10.1186/s13075-015-0706-2
63. Arrue I, Saiz A, Ortiz-Romero PL, Rodríguez-Peralto JL. Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol*. 2007;34(s1):18–21. http://dx.doi.org/10.1111/j.1600-0560.2007.00715.x
64. Yin Q, Xu X, Lin Y, Lv J, Zhao L, He R. Ultraviolet B irradiation induces skin accumulation of plasmacytoid dendritic cells: A possible role for chemerin. *Autoimmunity*. 2014;47(3):185–192. http://dx.doi.org/10.3109/08916934.2013.866105
65. Safi R, Al-Hage J, Abbas O, Kibbi A-G, Nassar D. Investigating the presence of neutrophil extracellular traps in cutaneous lesions of different subtypes of lupus erythematosus. *J Am Acad Dermatol*. 2019;28(11):1348–1352. http://dx.doi.org/10.1111/exd.14040
66. Kreuter A, Jaouhar M, Skrygan M, et al. Expression of antimicrobial peptides in different subtypes of cutaneous lupus erythematosus. *J Am Acad Dermatol*. 2011;65(1):125–133. http://dx.doi.org/10.1016/j.jaad.2010.12.012
67. Wooley PH, Seibold JR, Whalen JD, Chapdelaine JM. Pristane-induced arthritis. the immunologic and genetic features of an experimental murine model of autoimmune disease. *Arthritis Rheum*. 1989;32(8):1022–1030. http://dx.doi.org/10.1002/anr.1780320812
68. Chi Z, Wang Z, Wang K, Zhu Y, Qin S. Cathelicidin Antimicrobial Peptide LL-37 in Cholesteatoma Enables Keratinocyte Reactivity with Cytosolic DNA. *Scand J Immunol*. 2014;79(3):214–221. http://dx.doi.org/10.1111/sji.12149
69. Freutel S, Gaffal E, Zahn S, Bieber T, Tüting T, Wenzel J. Enhanced CCR5+/CCR3+ T helper cell ratio in patients with

active cutaneous lupus erythematosus. *Lupus*. 2011;20(12):1300–1304. http://dx.doi.org/10.1177/0961203311409267

70. Cole KE, Strick CA, Paradis TJ, et al. Interferon–inducible T Cell Alpha Chemoattractant (I-TAC): A Novel Non-ELR CXC Chemokine with Potent Activity on Activated T Cells through Selective High Affinity Binding to CXCR3. *J Exp Med*. 1998;187(12):2009–2021. http://dx.doi.org/10.1084/jem.187.12.2009
71. Dustin ML, Singer KH, Tuck DT, Springer TA. Adhesion of T lymphoblasts to epidermal keratinocytes is regulated by interferon gamma and is mediated by intercellular adhesion molecule 1 (ICAM-1).. *J Exp Med*. 1988;167(4):1323–1340. http://dx.doi.org/10.1084/jem.167.4.1323
72. Loetscher P, Pellegrino A, Gong J-H, et al. The Ligands of CXC Chemokine Receptor 3, I-TAC, Mig, and IP10, Are Natural Antagonists for CCR3. *J Biol Chem*. 2001;276(5):2986–2991. http://dx.doi.org/10.1074/jbc.m005652200
73. Tanasescu C, Balanescu E, Balanescu P, et al. IL-17 in cutaneous lupus erythematosus. *Eur J Intern Med*. 2010;21(3):202–207. http://dx.doi.org/10.1016/j.ejim.2010.03.004
74. Zúñiga LA, Jain R, Haines C, Cua DJ. Th17 cell development: from the cradle to the grave. *Immunol Rev*. 2013;252(1):78–88. http://dx.doi.org/10.1111/imr.12036
75. Oh SH, Roh HJ, Kwon JE, Lee SH, Kim JY, Choi HJ, Lim BJ. Expression of interleukin-17 is correlated with interferon-α expression in cutaneous lesions of lupus erythematosus. *Clin Exp Dermatol*. 2011;36(5):512–520. http://dx.doi.org/10.1111/j.1365-2230.2010.03996.x
76. Jabbari A, Suárez-Fariñas M, Fuentes-Duculan J, et al. Dominant Th1 and Minimal Th17 Skewing in Discoid Lupus Revealed by Transcriptomic Comparison with Psoriasis. *J Invest Dermatol*. 2014;134(1):87–95. http://dx.doi.org/10.1038/jid.2013.269
77. Quintana FJ, Basso AS, Iglesias AH, et al. Control of Treg and TH17 cell differentiation by the aryl hydrocarbon receptor. *Nature*. 2008;453(7191):65–71. http://dx.doi.org/10.1038/nature06880
78. Nistala K, Wedderburn LR. Th17 and regulatory T cells: rebalancing pro- and anti-inflammatory forces in autoimmune arthritis. *Rheumatology*. 2009;48(6):602–606. http://dx.doi.org/10.1093/rheumatology/kep028
79. Kishimoto T, Nguyen NT, Nakahama T, et al. Aryl hydrocarbon receptor antagonism and its role in rheumatoid arthritis. *J Exp Pharmacol*. 2015;1(7):29–35. http://dx.doi.org/10.2147/jep.s63549
80. Yu H, Jiang L, Liu R, et al. Association between the ratio of aryl hydrocarbon receptor (AhR) in Th17 cells to AhR in Treg cells and SLE skin lesions. *Int Immunopharmacol*. 2019;69:257–262. http://dx.doi.org/10.1016/j.intimp.2019.01.039
81. Batista FD, Harwood NE. The who, how and where of antigen presentation to B cells. *Nat Rev Immunol*. 2009;9(1):15–27. http://dx.doi.org/10.1038/nri2454
82. Wouters CHP, Diegenant C, Ceuppens JL, Degreef H, Stevens EAM. The circulating lymphocyte profiles in patients with discoid lupus erythematosus and systemic lupus erythematosus suggest a pathogenetic relationship. *Br J Dermatol*. 2004;150(4):693–700. http://dx.doi.org/10.1111/j.0007-0963.2004.05883.x
83. O'Brien JC, Hosler GA, Chong BF. Changes in T cell and B cell composition in discoid lupus erythematosus skin at different stages. *J Dermatol Sci*. 2017;85(3):247–249. http://dx.doi.org/10.1016/j.jdermsci.2016.12.004
84. Davidson A. Targeting BAFF in autoimmunity. *Curr Opin Immunol*. 2010;22(6):732–739. http://dx.doi.org/10.1016/j.coi.2010.09.010
85. Wenzel J, Landmann A, Vorwerk G, Kuhn A. High expression of B lymphocyte stimulator in lesional keratinocytes of patients with cutaneous lupus erythematosus. *Exp Dermatol*. 2018;27(1):95–97. http://dx.doi.org/10.1111/exd.13419
86. Thorpe RB, Gray A, Kumar KR, Susa JS, Chong BF. Site-Specific Analysis of Inflammatory Markers in Discoid Lupus Erythematosus Skin. *Sci World J*. 2014;2014 1–12. http://dx.doi.org/10.1155/2014/925805
87. Grassi M, Capello F, Bertolino L, Seia Z, Pippione M. Identification of granzyme B-expressing CD-8-positive T cells in lymphocytic inflammatory infiltrate in cutaneous lupus erythematosus and in dermatomyositis. *Clin Exp Dermatol*. 2009;34(8):910–914. http://dx.doi.org/10.1111/j.1365-2230.2009.03297.x
88. Jacquemin C, Augusto J, Scherlinger M, et al. OX40L/OX40 axis impairs follicular and natural Treg function in human SLE. *JCI Insight*. 2018;3(24):e122167. http://dx.doi.org/10.1172/jci.insight.122167
89. Dejaco C, Duftner C, Grubeck-Loebenstein B, Schirmer M. Imbalance of regulatory T cells in human autoimmune diseases. *Immunology*. 2006;117(3):289–300. http://dx.doi.org/10.1111/j.1365-2567.2005.02317.x
90. Campbell DJ, Koch MA. Phenotypical and functional specialization of FOXP3+ regulatory T cells. *Nat Rev Immunol*. 2011;11(2):119–130. http://dx.doi.org/10.1038/nri2916
91. Franz B, Fritzsching B, Riehl A, et al. Low number of regulatory T cells in skin lesions of patients with cutaneous lupus erythematosus. *Arthritis Rheum*. 2007;56(6):1910–1920. http://dx.doi.org/10.1002/art.22699
92. Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. *Nat Immunol*. 2009;10(8):857–863. http://dx.doi.org/10.1038/ni.1767
93. Fujita H. The role of IL-22 and Th22 cells in human skin diseases. *J Dermatol Sci*. 2013;72(1):3–8. http://dx.doi.org/10.1016/j.jdermsci.2013.04.028
94. Wolk K, Witte E, Wallace E, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. *Eur J Immunol*. 2006;36(5):1309–1323. http://dx.doi.org/10.1002/eji.200535503
95. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 Increases the Innate Immunity of Tissues. *Immunity*. 2004;21(2):241–254. http://dx.doi.org/10.1016/j.immuni.2004.07.007
96. Nograles KE, Zaba LC, Shemer A, et al. IL-22–producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17–producing TH17 T cells. *J Allergy Clin Immunol*. 2009;123(6):1244–1252.e2. http://dx.doi.org/10.1016/j.jaci.2009.03.041
97. Méndez-Flores S, Hernández-Molina G, Enríquez AB, et al. Cytokines and Effector/Regulatory Cells Characterization in the Physiopathology of Cutaneous Lupus Erythematous: A Cross-Sectional Study. *Mediators Inflamm*. 2016;2016:1–15. http://dx.doi.org/10.1155/2016/7074829
98. Zahn S, Graef M, Patsinakidis N, et al. Ultraviolet light protection by a sunscreen prevents interferon-driven skin inflammation in cutaneous lupus erythematosus. *Exp Dermatol*. 2014;23(7):516–518. http://dx.doi.org/10.1111/exd.12428

99. Grönhagen CM, Tang MBY, Tan VWD, Tan KW, Lim YL. Vitamin D levels in 87 Asian patients with cutaneous lupus erythematosus: a case-control study. *Clin Exp Dermatol*. 2016;41(7):723–729. http://dx.doi.org/10.1111/ced.12884
100. White PC, Hirschfeld J, Milward MR, Cooper PR, Wright HJ, Matthews JB, Chapple ILC. Cigarette smoke modifies neutrophil chemotaxis, neutrophil extracellular trap formation and inflammatory response-related gene expression. *J Periodontal Res*. 2018;53(4):525–535. http://dx.doi.org/10.1111/jre.12542
101. Guicciardi F, Atzori L, Marzano AV, et al. Are there distinct clinical and pathological features distinguishing idiopathic from drug-induced subacute cutaneous lupus erythematosus? A European retrospective multicenter study. *J Am Acad Dermatol*. 2019;81(2):403–411. http://dx.doi.org/10.1016/j.jaad.2019.02.009
102. Laurinaviciene R, Sandholdt LH, Bygum A. Drug-induced cutaneous lupus erythematosus: 88 new cases. *Eur J Dermatol*. 2017;27(1):28–33. http://dx.doi.org/10.1684/ejd.2016.2912
103. Okon LG, Werth VP. Cutaneous lupus erythematosus: Diagnosis and treatment. *Best Pract Res Clin Rheumatol*. 2013;27(3):391–404. http://dx.doi.org/10.1016/j.berh.2013.07.008
104. Cavazzana I, Sala R, Bazzani C, et al. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. *Lupus*. 2009;18(8):735–739. http://dx.doi.org/10.1177/0961203308101714
105. Chasset F, Bouaziz J-D, Costedoat-Chalumeau N, Francès C, Arnaud L. Efficacy and comparison of antimalarials in cutaneous lupus erythematosus subtypes: a systematic review and meta-analysis. *Br J Dermatol*. 2017;177(1):188–196. http://dx.doi.org/10.1111/bjd.15312
106. Chang J, Werth VP. Therapeutic options for cutaneous lupus erythematosus: recent advances and future prospects. *Expert Rev Clin Immunol*. 2016;12(10):1109–1121. http://dx.doi.org/10.1080/1744666x.2016.1188006
107. Yokogawa N, Eto H, Tanikawa A, et al. Effects of Hydroxychloroquine in Patients With Cutaneous Lupus Erythematosus: A Multicenter, Double-Blind, Randomized, Parallel-Group Trial. *Arthritis Rheumatol*. 2017;69(4):791–799. http://dx.doi.org/10.1002/art.40018
108. Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). *Expert Opinion on Drug Safety*. 2017;16(3):411–419. http://dx.doi.org/10.1080/14740338.2017.1269168
109. Gardet A, Pellerin A, McCarl C-A, et al. Effect of in vivo Hydroxychloroquine and ex vivo Anti-BDCA2 mAb Treatment on pDC IFNα Production From Patients Affected With Cutaneous Lupus Erythematosus. *Front Immunol*. 2019;10:275. http://dx.doi.org/10.3389/fimmu.2019.00275
110. Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. *Arthritis Res Ther*. 2012;14(3):R155. http://dx.doi.org/10.1186/ar3895
111. Alves P, Bashir MM, Wysocka M, Zeidi M, Feng R, Werth VP. Quinacrine Suppresses Tumor Necrosis Factor-α and IFN-α in Dermatomyositis and Cutaneous Lupus Erythematosus. *J Investig Dermatol Symp Proc*. 2017;18(2):S57–S63. http://dx.doi.org/10.1016/j.jisp.2016.11.001
112. Sperber K, Quraishi H, Kalb TH, Panja A, Stecher V, Mayer L. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. *Journal Rheum*. 1993;20(5):803–808. https://www.ncbi.nlm.nih.gov/pubmed/8336306
113. Wakiya R, Kameda T, Ueeda K, et al. Hydroxychloroquine modulates elevated expression of S100 proteins in systemic lupus erythematosus. *Lupus*. 2019;28(7):826–833. http://dx.doi.org/10.1177/0961203319846391
114. Takezawa K, Ueda-Hayakawa I, Yamazaki F, Kambe N, Son Y, Okamoto H. Successful treatment with hydroxychloroquine for systemic lupus erythematosus with cutaneous involvement accompanied by a xanthomatous reaction. *Lupus*. 2020;29(1):79–82. http://dx.doi.org/10.1177/0961203319890677
115. Kuhn A, Gensch K, Haust M, et al. Efficacy of tacrolimus 0.1% ointment in cutaneous lupus erythematosus: A multicenter, randomized, double-blind, vehicle-controlled trial. *J Am Acad Dermatol*. 2011;65(1):54–64. http://dx.doi.org/10.1016/j.jaad.2010.03.037
116. Sigmundsdottir H, Johnston A, Gudjonsson JE, Bjarnason B, Valdimarsson H. Methotrexate markedly reduces the expression of vascular E-selectin, cutaneous lymphocyte-associated antigen and the numbers of mononuclear leucocytes in psoriatic skin. *Exp Dermatol*. 2004;13(7):426–434. http://dx.doi.org/10.1111/j.0906-6705.2004.00177.x
117. Wenzel J, Brahler S, Bauer R, Bieber T, Tuting T. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol*. 2005;153(1):157–162. http://dx.doi.org/10.1111/j.1365-2133.2005.06552.x
118. Boehm IB, Boehm GA, Bauer R. Management of cutaneous lupus erythematosus with low-dose methotrexate: indication for modulation of inflammatory mechanisms. *Rheumatol Int*. 1998;18(2):59–62. http://dx.doi.org/10.1007/s002960050058
119. Kuhn A, Specker C, Ruzicka T, Lehmann P. Methotrexate treatment for refractory subacute cutaneous lupus erythematosus. *J Am Acad Dermatol*. 2002;46(4):600–603. http://dx.doi.org/10.1067/mjd.2002.114608
120. Furie R, Werth VP, Merola JF, et al. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. *J Clin Invest*. 2019;129(3):1359–1371. http://dx.doi.org/10.1172/jci124466
121. Hofmann SC, Leandro MJ, Morris SD, Isenberg DA. Effects of rituximab-based B-cell depletion therapy on skin manifestations of lupus erythematosus – report of 17 cases and review of the literature. *Lupus*. 2013;22(9):932–939. http://dx.doi.org/10.1177/0961203313497115
122. Vital EM, Wittmann M, Edward S, et al. Brief Report: Responses to Rituximab Suggest B Cell-Independent Inflammation in Cutaneous Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2015;67(6):1586–1591. http://dx.doi.org/10.1002/art.39085
123. Vashisht P, Borghoff K, O'Dell JR, Hearth-Holmes M. Belimumab for the treatment of recalcitrant cutaneous lupus. *Lupus*. 2017;26(8):857–864. http://dx.doi.org/10.1177/0961203316682097
124. Khamashta M, Merrill JT, Werth VP, et al. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis*. 2016;75(11):1909–1916. http://dx.doi.org/10.1136/annrheumdis-2015-208562
125. Werth VP, Fiorentino D, Sullivan BA, et al. Brief Report: Pharmacodynamics, Safety, and Clinical Efficacy of AMG 811, a Human Anti–Interferon-γ Antibody, in Patients With Discoid Lupus Erythematosus. *Arthritis Rheumatol*. 2017;69(5):1028–1034. http://dx.doi.org/10.1002/art.40052

126. Petri M, Wallace DJ, Spindler A, et al. Sifalimumab, a Human Anti-Interferon-α Monoclonal Antibody, in Systemic Lupus Erythematosus: A Phase I Randomized, Controlled, Dose-Escalation Study. *Arthritis Rheumatol*. 2013;65(4):1011–1021. http://dx.doi.org/10.1002/art.37824
127. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2017;69(2):376–386. http://dx.doi.org/10.1002/art.39962
128. Illei GG, Shirota Y, Yarboro CH, e al. Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheumatol*. 2010;62(2):542–552. http://dx.doi.org/10.1002/art.27221
129. Makol A, Gibson LE, Michet CJ. Successful Use of Interleukin 6 Antagonist Tocilizumab in a Patient With Refractory Cutaneous Lupus and Urticarial Vasculitis. *J Clin Rheumatol*. 2012;18(2):92–95. http://dx.doi.org/10.1097/rhu.0b013e31823ecd73
130. Rovin BH, van Vollenhoven RF, Aranow C, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Treatment With Sirukumab (CNTO 136) in Patients With Active Lupus Nephritis. *Arthritis Rheumatol*. 2016;68(9):2174–2183. http://dx.doi.org/10.1002/art.39722
131. Llorente L, Richaud-Patin Y, García-Padilla C, et al. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. *Arthritis Rheumatol*. 2000;43(8):1790–1800. http://dx.doi.org/10.1002/1529-0131(200008)43:8<1790::aid-anr15>3.0.co;2-2
132. van Vollenhoven RF, Hahn BH, Tsokos GC, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet*. 2018;392(10155):1330–1339. http://dx.doi.org/10.1016/s0140-6736(18)32167-6
133. De Souza A. Successful Treatment of Subacute Lupus Erythematosus With Ustekinumab. *Arch Dermatol*. 2011;147(8):896–8. http://dx.doi.org/10.1001/archdermatol.2011.185
134. Winchester D, Duffin KC, Hansen C. Response to ustekinumab in a patient with both severe psoriasis and hypertrophic cutaneous lupus. *Lupus*. 2012;21(9):1007–1010. http://dx.doi.org/10.1177/0961203312441982
135. Romero-Mate A, Garcia-Donoso C, Hernandez-Nunez A, Martinez-Moran C, Moreno-Torres A, Borbujo-Martinez J. Successful treatment of recalcitrant discoid lupus erythematosus with ustekinumab. *Dermatol Online J*. 2017;23(1):13030/qt206538zm. https://www.ncbi.nlm.nih.gov/pubmed/28329473
136. Braegelmann C, Hölzel M, Ludbrook V, et al. Spleen tyrosine kinase (SYK) is a potential target for the treatment of cutaneous lupus erythematosus patients. *Exp Dermatol*. 2016;25(5):375–379. http://dx.doi.org/10.1111/exd.12986
137. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. *Nat Rev Rheumatol*. 2019;15(9):519–532. http://dx.doi.org/10.1038/s41584-019-0272-0
138. Wieczorek IT, Propert KJ, Okawa J, Werth VP. Systemic Symptoms in the Progression of Cutaneous to Systemic Lupus Erythematosus. *JAMA Dermatology*. 2014;150(3):291–6. http://dx.doi.org/10.1001/jamadermatol.2013.9026
139. Deng G-M. Pathogenesis of Skin Injury of Systemic Lupus Erythematosus. *Curr Rheumatol Rep*. 2018;20(2):5. http://dx.doi.org/10.1007/s11926-018-0713-9

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