

Cutaneous Lupus

Insights into Pathogenesis and Disease Classification

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Abstract

Skin disease is the second most common manifestation in SLE patients, and a large number of patients have predominantly cutaneous lupus erythematosus. Experimental animal models suggest that modulation of immunologic factors can have a differential impact on the skin relative to the kidney, and therapeutic responses also suggest potential differences in the immunomodulation of skin relative to other organs affected in lupus. There have been recent insights into the etiology of cutaneous LE, including genetic and environmental factors. The growing understanding of the inflammatory cascade includes the role of UV-induction of pro-inflammatory cytokines, chemokines, and adhesion molecules. Apoptosis, necrosis, autoantibodies, plasmacytoid dendritic cells, T cells, B cells, and vascular changes all play a complex interactive role in the process of induction and maintenance of the lesions of cutaneous LE. Scientific efforts are beginning to clarify the pathophysiologic differences between subsets of cutaneous LE, but there are clearly many areas of investigation needed to elucidate the complex mechanisms that culminate in cutaneous LE.

Cutaneous variants of lupus erythematosus (LE) may occur two to three times more frequently than systemic lupus erythematosus (SLE), and not infrequently is associated with vocational disability.¹ Skin disease is the second most common manifestation in SLE patients. There have been recent insights into cutaneous LE, including genetic and environmental factors. Triggering factors include ultraviolet light, medications, hormones, stress, viruses, and skin trauma. The growing understanding of the inflammatory

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cascade includes new insights into the role of UV-induction of pro-inflammatory cytokines, chemokines, and adhesion molecules. Apoptosis, necrosis, autoantibodies, plasmacytoid dendritic cells, T cells, B cells, and vascular changes all play a role in the process of induction of the lesions of cutaneous LE. A review of the advances in understanding of the pathogenesis and the implications for cutaneous subsets of LE will be reviewed.

Cutaneous Lupus Erythematosus

Although clearly there is a link between the skin and systemic manifestations of LE, often the skin may flare independently or patients may have SLE without skin disease. Treatments also may improve the skin, systemic disease, or both, suggesting that there are differences pathogenetically between skin and systemic findings in LE.

Experimental models suggest that lupus-associated end-organ disease in skin versus kidneys occurs by independent pathways in MRL/lpr mice lacking specific immunoregulatory genes. For instance, CD40L-deficient MRL/lpr mice acquire mild renal disease, but no change in skin disease.² MRL/lpr mice deficient in B₂-macroglobulin develop reduced kidney disease but exacerbated skin disease.³ Therapies that improve skin disease may have no or minimal effects on systemic disease, both in mice and humans.^{4,5} Thus, it is important to understand the specific pathophysiologic pathways involved in cutaneous LE.

Genetics and Cutaneous LE

There is an association of subacute cutaneous LE (SCLE) with the extended HLA haplotype DRB1*0301-B*08.⁶ Contained within this haplotype is the TNF2 allele, the -308A TNF α promoter polymorphism, and it is clear that this haplotype is associated with increased TNF α production.^{7,8} Whether TNF2 has a primary independent association or arises as a consequence of linkage with HLA genes is more

difficult. Studies continue to explore whether there is an independent association of TNF2 with SLE.⁹ It is of interest that high titer anti-SSA autoantibodies are associated with HLA-DR3 and SCLE, and that the linkage of TNF2 with HLA-DR3 in SCLE patients is much tighter than that seen in control or dermatomyositis patients.¹⁰ Neonatal LE has a similar genetic predisposition to SCLE.¹¹

Other genetic associations with cutaneous LE include patients with C1q deficiency, who frequently develop LE-like photosensitive eruptions.¹² C2 and C4 deficiencies are associated with SCLE. While complement deficiencies are less common in discoid lupus (DLE), C1 inhibitor, C1q, C2, and partial C4b deficiencies have been observed. There is evidence that C1q binds apoptotic cells and may play a role in clearance of apoptotic keratinocytes.¹³ Increased numbers of apoptotic and possibly necrotic cells, either from an excessive amount of death induction by UV or due to cytotoxic effects of inflammatory cells, or from a defect in clearance of apoptotic cells, could break tolerance to self-antigens.

Given the association of SCLE, but not DLE, with the extended HLA haplotype DRB1*0301-B*08, it is certain that predisposition to specific subsets of cutaneous LE is related to different genes. Another indication of this is the recent characterization of a genetic locus associated with familial chilblain lupus that mapped to chromosome 3p.¹⁴ Given the number of genes in the mapped area, even in this large well-characterized kindred, it is clear that determination of the exact genetic abnormalities associated with cutaneous forms of LE is a challenge.

Triggers of Cutaneous LE

There are multiple triggers of subsets of cutaneous LE. Clearly SCLE and tumid LE are the most photosensitive subsets.¹⁵⁻¹⁷ Phototesting studies suggest that both UVB and UVA are potentially pathogenic wavelengths, although it is clear that UVA induction requires higher doses of light relative to UVB. In addition, phototesting does not universally induce lesions, and experience has led to recommended testing of the upper back or arm skin in large surface areas.^{15,18}

Medications are a frequent trigger of subacute cutaneous LE (SCLE). Patients with SCLE should be carefully screened to make sure there has not been the addition of a new medication or that the patient is not taking one of the many potentially triggering medications.⁹ It is clear that hormones must play a significant role in SCLE relative to DLE, with some studies reporting an 8.5:1 ratio of females to males in SCLE, but closer to a 1:1 ratio in DLE.^{6,20} On the other hand, smoking is seen more frequently in patients with DLE compared to controls.²¹

Ultraviolet Light-Induced Apoptosis/Necrosis

Ultraviolet irradiation of skin can induce apoptosis and, at higher doses, necrosis of cells. UV light can induce the

binding of autoantibodies, such as Ro/SSA and La/SSB, to selected nuclear antigens located on blebs or apoptotic bodies of skin and cultured human keratinocytes.²²⁻²⁴ It has been suggested that these bleb-associated antigens may then be phagocytosed, packaged, and presented to lymphocytes, thereby stimulating autoimmune responses.^{25,26}

There appears to be a minimal, if any, decrease in the minimal erythema dose in SLE or SCLE.^{18,27} In addition, there is controversy about whether the actual number of apoptotic cells is increased in irradiated normal skin of LE patients relative to controls.^{27,28} Lesional cutaneous LE skin does demonstrate increased numbers of apoptotic cells and has been associated with increased p53 protein expression.^{29,30} The nuclear phosphoprotein p53 is a tumor suppressor that is upregulated in response to UV-induced DNA damage³¹ and in response to TNF- α and interferon- γ (IFN- γ).^{32,33} Upregulation of p53 in suprabasilar keratinocytes can initiate cell death by apoptosis.³⁴ The increased number of apoptotic cells, therefore, could be a result of an increased rate of apoptosis induction, mediated directly by UV light or as a consequence of UV-induced cytokine release. Apoptosis also can be induced by cellular cytotoxic mechanisms. Cytotoxic T lymphocytes (CTL) and natural killer (NK) cells can induce apoptosis through multiple mechanisms, including the release of perforin and granzymes, cytokine release [IFN- γ , tumor necrosis factor (TNF)- α , TNF- α , interleukin (IL)-1], and triggering of Fas by FasL.^{32,35-37} The presence of leukocytes in proximity to the apoptotic cells and the presence of FasL positive macrophages in proximity to apoptotic cells in lesional hair follicles suggest a role for such cellular apoptotic mechanisms in established lesions.^{38,39}

Autoantibodies can initiate cellular cytotoxicity, and it would appear that anti-SSA and anti-SSB antibodies may function this way.⁴⁰ One study suggests that Ro is involved in a quality control pathway for 5S ribosome RNA.⁴¹ Genetic knock-out of 60kD Ro resulted in an SLE-like illness in multiple strains of mice that were susceptible to UV damage.⁴² It is possible that anti-Ro antibodies might interfere with protection from UV damage. The role of autoantibodies in DLE is less clear, and patients with tumid LE frequently do not have demonstrable serum autoantibodies.

What is clear is that UVB can induce a proinflammatory cascade of events in the skin. Exposure of keratinocytes to UVB results in the synthesis of many cytokines, including tumor necrosis factor- α (TNF- α),^{43,44} interleukin-1 α (IL-1 α), IL-6, IL-8, and IL-10.^{45,46} TNF- α is not only involved in the mediation of local inflammatory reactions within the epidermis, but may also enter the circulation and cause systemic effects.^{43,47} There are chemokines and adhesion molecules stimulated by these inflammatory cytokines.⁴⁸ Ultraviolet light induces CCL27 (cutaneous T cell-attracting chemokine) and CCL20 (macrophage inflammatory protein 3 α), an important chemokine for Langerhans cells, as well as CCL2 and CCL5.⁴⁹ The initial chemokine production and release results in a first wave of skin-homing memory T cells

and plasmacytoid dendritic cells (PDCs) via CCR5-, CCR6-, and CCR10-driven pathways to sites of UV-induced injury. In cutaneous LE, activated PDCs and T cells in the skin secrete cytokines, in particular IFN- α , IFN- γ , IL-1 α , and TNF α , with expression of the IFN α -inducible genes IRF7 and MxA, that subsequently induce a different set of chemokines.⁵⁰⁻⁵² DNA, RNA, and immune complexes, present in skin containing apoptotic cells from UV or cytotoxic cells, can serve as IFN- α inducers. Sequencing of TCR clonotypes from skin suggests an antigen driven response.⁵³ In addition, there is evidence of costimulation of T cells by CD80/86 on APCs that interact with CD28 and CTLA-4 on T cells.⁵⁴

IFN α induces unabated activation of PDCs, which select and activate autoreactive T cells rather than deleting them, thus failing to induce peripheral tolerance. Enhanced type I IFN signaling promotes Th1-biased inflammation in cutaneous LE.⁵² IFN α is a potent and rapid inducer of CXCR3 ligands in the inflammatory cells in the skin. In established cutaneous LE lesions, the CXCR3 ligands CXCL9 (interferon-gamma [IFN γ]-induced monokine), CXCL10 (IFN γ -inducible protein 10), and CXCL11 (IFN-inducible T cell alpha chemoattractant) are the most abundantly expressed chemokine family members.^{49,55} Large numbers of infiltrating CXCR3+ lymphocytes are detected in cutaneous LE skin lesions.⁵¹ In addition, interaction between CCR4 and its ligand TARC/CCL17 on activated endothelial cells mediates T cell extravasation by stimulating integrin-dependent adhesion of CLA+ T cells to ICAM-1.⁵⁶ There are increased TARC/CCL17 and CCR4 in the skin and blood of all cutaneous LE patients, but one recent study suggests circulating and lesional CD8+ T lymphocytes expressing CLA and CCR4 are seen specifically in scarring forms of cutaneous LE.⁵⁷ Granzyme B is seen in greater quantities in lesional lymphocytes of patients with scarring DLE skin lesions, as opposed to SCLE, and the numbers of cytotoxic T cells is less in SCLE than DLE.⁵² There are clearly changes in the circulating T cells of patients with cutaneous LE. In particular, the highest percentage of HLA-DR expression was found on CD4+ T cells in patients with active SCLE and disseminated DLE.⁵⁸ IFN also stimulates B Cells, ICs bind to the Fc γ receptor, and Toll receptors provide an amplification loop for IFN production and B-cell activation.

Vessel changes are important in cutaneous LE, and there is evidence of induction of adhesion molecules in vessels, as outlined above. In addition, nitric oxide is upregulated in the endothelial cells of patients with both cutaneous and systemic LE, particularly after UV irradiation.^{59,60}

Subsets and Pathophysiology

The clinical and pathologic differences between subsets of cutaneous LE have become more clear in recent years.^{61,62} It is now becoming possible to dissect the complex interplay of genetics, environment, autoantibodies, inflammatory cytokines, chemokines, and adhesion molecules, as well as the subsequent homing of inflammatory cells to the skin that

likely account for the many differences observed in patients with cutaneous LE.

As discussed above, there are distinct genetics associated with subacute cutaneous LE. Patients frequently have more than one subset of cutaneous LE, as demonstrated by the frequent concurrence of discoid LE and lupus panniculitis, even in the same lesion. Inflammatory cells with their own molecules home to specific locations in the skin dictated by cytokine, chemokine, and adhesion molecule expression.^{49-52,55,56} Many patients with bullous LE have circulating anti-Type VII collagen antibodies that bind to the basement membrane, causing a dermal-epidermal split and formation of the bullae.⁶³⁻⁶⁵

Treatment with UVA1

There is growing evidence that low-dose UVA1 therapy, usually doses from 5 to 8 J/cm², can be beneficial for photosensitive forms of cutaneous LE, including decreasing anti-SSA antibodies.^{66,67} Although the mechanism is still not certain, IL-12 can induce DNA repair,^{68,69} and UVA1 can induce IL-12 in the absence of induction of other UVB-induced inflammatory cytokines.^{68,70} It is clear that higher doses of UVA can cause photoinduction of lesions, and, thus, further studies are warranted to systematically evaluate the potential role of UVA1 treatment.^{15,71}

Conclusion

We are developing a greater understanding of the pathogenesis of cutaneous LE. Scientific efforts are beginning to clarify the pathophysiologic differences between subsets of cutaneous LE, but there are clearly many areas of investigation needed to elucidate the complex mechanisms that culminate in cutaneous LE.

Disclosure Statement

The author does not have a financial or proprietary interest in the subject matter or materials discussed in the manuscript, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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