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The Immunology of Cutaneous Lupus Erythematosus

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The immunologic mechanisms involved in cutaneous lupus erythematosus are closely tied to the histologic and ultrastructural changes seen at the dermo-epidermal junction. These alterations are reviewed and an attempt is made to interrelate them with the current ideas on pathogenesis and therapy.

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HISTOLOGY AND ULTRASTRUCTURE OF THE DERMO-EPIDERMAL JUNCTION

The basement membrane region of skin lesions in lupus erythematosus patients has been the focus of considerable interest since the discovery that it appears thickened in histological sections, especially when stained with the periodic-acid-Schiff stain (1). With the advent of immunofluorescence it became apparent that immunoglobulins and complement are deposited in the same area, not only in the lesional skin of many lupus erythematosus patients, but also on the non-lesional skin of patients with systemic lupus erythematosus (lupus band). The deposition is granular or fibrillar at the basement membrane zone when it is examined with the immunofluorescence microscope after staining with the appropriate fluorescein isothiocyanate conjugated anti-human immunoglobulin (usually IgG or IgM, less commonly IgA) and complement (2, 3).

Electron microscopy later revealed that the deposition of the immunoglobulins was located on and below the lamina densa of the basement membrane in the skin of lupus erythematosus patients (3). The components of the lamina densa are type IV collagen, heparan sulfate proteoglycan, chondroitin-6-sulfate proteoglycan, nidogen and two antigens designated by the abbreviations KF-1 and LDA-1 for their respective antibodies (4). It has now become apparent that the anchoring fibrils are composed of type VII collagen, and the carboxyl terminus of the molecule, which is located in the lamina densa, is recognized by the LH7:2 and epidermolysis bullosa acquisita antibodies (5, 6) (Table I). Through the use of electron microscopy it also became evident that the basement membrane thickening seen on periodic-acid-Schiff staining with light microscopy corresponded to reduplication of the lamina densa of the basement membrane. Moreover, disruption of the basal cells of the epidermis was observed (Table II) (7).

Table I. *Antigens in the basement membrane zone*

Lamina lucida
Laminin
Bullous pemphigoid antigen
Cicatricial pemphigoid antigen
GB3
Lamina densa
Type IV collagen
Type VII collagen
Heparan sulfate proteoglycan
Chondroitin-6-sulfate proteoglycan
LDA-1
KF-1
Nidogen
(Fibronectin)

Table II. *Histologic and ultrastructural changes at the basement membrane zone*

Histology	Immunofluorescence	Ultrastructure
Thickening (especially on periodic-acid-Schiff staining)	IgG IgM C3 (IgA) granular or fibrillar	Reduplication of lamina densa with immunoglobulins on and below the lamina densa

CHANGES IN MATRIX MOLECULES

Our work examining the status of six matrix molecules at the basement membrane zone in lupus erythematosus patients using monoclonal antibodies and immunofluorescent microscopy in biopsies from 37 patients and immunoelectron microscopy of four patients revealed that type IV and type VII collagen, which are both components of the lamina densa, showed considerable alteration in the lesional skin of lupus patients. There was also a statistically significant correlation between the presence of immunoglobulin deposition and alteration of collagen types IV and VII in the lesional skin when examined by immunofluorescence. The changes in type IV and type VII collagen consisted of non-linearity of staining in the form of fragmentation of both antigenic components (Table III). This fragmentation was also seen when the biopsies were examined with immunoelectron microscopy and was more pronounced in type IV collagen. Additionally, there was reduplication of type VII collagen and, in some instances, stained fragments were noted below the lamina densa (8).

Table III. *Changes in matrix molecules*

Indirect immunofluorescence	
	All specimens
Linear vs non-linear staining in lesional and non-lesional skin	Probability of a greater value on χ^2 with 1 DF
Type IV collagen	$0.02 > P > 0.01$
Type VII collagen	$P < 0.001$
Fibronectin	$0.005 > P > 0.001$
	Lesional skin
Linear vs non-linear staining and immunoglobulin deposition	Probability of a greater value on χ^2 with 1 DF
Type IV collagen	$P < 0.001$
Type VII collagen	$P < 0.001$

PATHOGENESIS

The initiating event leading to epidermal cell damage and subsequent antibody formation to antigens made available at the cell surface by this damage may be the immune complex deposition at the basement membrane zone, which can be experimentally induced by ultraviolet light (8). The immune complexes can generate assembly of the so-called membrane attack complex of complement, C5b-C9, which mediates membrane injury (9) such as that seen in the epidermal cells of lupus erythematosus skin lesions. During the course of the skin disease, an infiltrate occurs at the basement membrane zone, adding credence to the theory that antibody-dependent cellular cytotoxicity may play a part in the pathogenesis (10). The inflammatory infiltrate and its constituent cytokines such as interleukin-1 cause increased production of collagenases capable of causing disruption of the collagen components of the lamina densa such as type IV and VII collagen. Levels of interleukin-1 are also increased during ultraviolet exposure, potentially causing increased damage (11) and there is recent evidence supporting mediation by cutaneous interleukin-1 of ultraviolet induced exacerbation in lupus erythematosus (13).

THERAPY

From the afore-mentioned, the use of sunscreens, anti-inflammatory agents such as steroids and other immune suppressants appears quite rational although the effects of the latter two are not specifically directed and have numerous side-effects. Currently the retinoids are receiving some interest since they appear helpful in cutaneous lupus, although it is still unknown how they aid. Possibilities include their anti-inflammatory effects (14), inhibition of polyclonal B-cell stimulation (15) or stimulation of macrophages aiding in elimination of inciting factors (16). Future efforts in treating cutaneous lupus might be directed against the various components instrumental in causing damage at the dermo-epidermal junction and continued research will give further insight into how this occurs.

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