

Invited Review

Antinuclear antibody-keratinocyte interactions in photosensitive cutaneous lupus erythematosus

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Summary. Autoimmune diseases are characterized by various circulating autoantibodies, especially antinuclear antibodies (ANA). It has been a long-standing issue as to whether and/or how ANA interact with epidermal cells to produce skin lesions. Of these ANA, the anti-SS-A/Ro antibody is the most closely associated with photosensitivity in patients with systemic lupus erythematosus (SLE) and its subgroups, including subacute cutaneous lupus erythematosus (SCLE) and neonatal lupus erythematosus (NLE). SS-A/Ro antigens are present in the nucleus and cytoplasm, and interestingly, ultraviolet B (UVB) light translocates these antigens to the surface of the cultured keratinocytes. Thus, anti-SS-A/Ro antibodies in the sera can bind to the relevant antigens expressed on the UVB-irradiated keratinocyte surface, and have been speculated to be an important inducer of antibody-dependent keratinocyte damage. This interaction between the anti-SS-A/Ro antibodies and UVB-irradiated keratinocytes may induce the skin lesions through a cytotoxic mechanism. This review will focus on the involvement of antibody-dependent cellular cytotoxicity in the pathogenesis of the skin lesions observed in photosensitive cutaneous lupus erythematosus.

Key words: Keratinocyte, Autoantibody, Photosensitivity, Lupus erythematosus, Antibody-dependent cellular cytotoxicity

Introduction

Systemic lupus erythematosus (SLE) is a multi-organ disease, and is characterized by the presence of circulating antinuclear antibodies (ANA) and immune complex-mediated tissue injuries. The skin is one of the major target organs, as well as the kidneys. Photosensitivity is a well-known phenomenon accompanying the skin lesions of SLE and its subtypes such as neonatal lupus erythematosus (NLE) and subacute cutaneous

lupus erythematosus (SCLE), and is very closely associated with the development of erythema.

Historically, Natali and Tan (1973) reported that mice immunized with UV-irradiated DNA showed skin lesions that clinically and immunohistologically resembled the skin lesions of human SLE after receiving whole-body UV-irradiation. Their report suggested that DNA-anti-DNA antibody immune complexes induce these skin lesions. Recently, severe form of UV-induced skin injury seen in humans could be reproduced in hairless descendants of Mexican hairless dogs exposed to high energy dose of artificial UVA+B (Ishii et al., 1997).

In human lupus erythematosus (LE), sunlight is known to induce or exacerbate the skin lesions and diseases in other organs (Zamansky, 1985). The mechanisms underlying photosensitivity in LE have been investigated ever since Epstein et al. (1965) first artificially induced skin lesions in patients with LE and photosensitivity. The initial reports suggested that the action spectrum for LE was in the UVB range (290-320nm wave length) (Freeman and Knox, 1969; Cripps and Rankin, 1973), but more recent studies have demonstrated that UVA (320-400nm) can contribute to the induction of LE skin lesions (Hozle, 1987). However, there has been a long-standing issue as to whether and/or how ANA interact with epidermal cells to produce skin lesions.

In this article, I focus on the interaction between ANA and keratinocyte damage in photosensitive cutaneous LE in order to better understand why erythematous lesions develop in the patients.

Clinical features of cutaneous lupus erythematosus

Skin lesions are variable in cutaneous LE; Table 1 shows 3 typical types of cutaneous LE such as SLE, discoid LR (DLE) and SCLE (Furukawa, 1998). The clinical entity of each type of cutaneous LE was based on their clinical features, serological findings and immunohistological findings. However, the classification and nomenclature of cutaneous LE remain unsettled because the cutaneous and systemic manifestations of LE are actually different patterns of

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clinical expression of the same underlying heterogeneous autoimmune disease process (Sontheimer, 1997).

In SLE, skin lesions are present in at least 80% of the patients, and are the primary sign in about 25% of these individuals. The most common presentation is the presence of erythema over the photolocalizing areas of the face, V region of the chest, extensors of the extremities, dorsa of the hands, and mid-upper back and shoulders. The erythematous lesions of SLE consist of erythematous, slightly edematous patches without significant scaling or without atrophy. In addition, discoid lesions described below are frequently observed in patients with SLE.

The characteristic features of SCLE are extensive, erythematous, symmetric nonscarring and non-atrophic lesions that arise abruptly on the upper trunk, extensor surfaces of the arms, and dorsa of the hands and fingers. These eruptions have two clinical variants: (1) papulo-squamous lesions; and (2) annular to polycyclic lesions. Photosensitivity is characteristic in SCLE, as well as erythematous lesions (Sontheimer et al., 1979). The histological changes are almost identical to those of SLE, but differ in degree and incidence (Jaworsky, 1997).

In DLE, the skin lesions consist of well-demarcated, erythematous, slightly infiltrated, "discoid" plaques that often show adherent thick scales and follicular plugging. The discoid lesions are limited to the face, where the malar areas and the nose are predominantly affected.

Histopathology and immunohistology of cutaneous lupus erythematosus

The histological findings are similar among the three types of cutaneous LE. The early lesions of SLE of the edematous erythema show non-specific changes. In well-developed lesions, the histological changes consist of: 1) liquefaction changes; 2) colloid bodies in the lower epidermis and papillary dermis; 3) edematous changes in the dermis; 4) extravasation of erythrocytes; 5) dermal fibrinoid deposits; and 6) mononuclear cell

infiltration in the dermis (Jaworsky, 1997). The incidence of each change, based on our observations of 62 cases, was 67.7% for the liquefaction change, 46.8% for atrophy of the epidermis, 56.5% for hyperkeratosis, 27.4% for hypergranulosis, 77.4% for lymphocyte infiltration in the dermis, 64.5% for edematous changes, 66.1% for fibrinoid deposits, 59.7% for vasodilatation, 12.9% for incontinence of the pigment and 21.0% for keratin plugging. SCLE shows almost identical changes, but differs in the degree and incidence of these findings (Jaworsky, 1997). Although the histological changes of DLE are similar to those of SLE and SCLE, their characteristics are patchy inflammatory infiltrates at all levels of the skin from the interface to the subcutaneous fat tissue.

Immunohistologically, these skin lesions are characteristic in the presence of immunoglobulin and complement components at the dermo-epidermal junction (DEJ). This is termed the lupus band test (LBT), and is one of the routine laboratory tests (Fig. 1). As shown in Table 1, a positive LBT is demonstrated in 80-90% of the erythematous lesions of SLE, and more importantly in 50% of the non-lesional skin of SLE. In contrast, the non-lesional skin of DLE shows no deposition of immunoreactants. Band-like or linear deposits of IgG and IgM are frequently demonstrated in the skin lesions of SLE and DLE. It is of interest to note that SCLE shows the presence of IgG in most cases, at the epidermal nucleus and DEJ with a fine granular pattern. These immunohistological findings suggest the presence of autoantibodies and/or immune complexes at the DEJ and/or epidermal keratinocytes.

Autoantibodies in cutaneous lupus erythematosus

Various types of autoantibodies are circulating in patients with autoimmune collagen diseases. However, the direct pathogenic effects on tissue injury remain unclear, except for anti-DNA antibody-mediated vascular endothelial damage and anti-SS-A/Ro antibody-mediated keratinocyte damage. The pathogenic relationships were deduced from the association between the

Table 1. Characteristics of cutaneous lupus erythematosus.

	SLE	DLE	SCLE
Age of onset	20-30 y	20-60 y	40-50 y
Gender (F/M)	9/1	2/1	7/3
Erythema	slight edematous or discoid pathes	discoid pathes	annular or papulosquamous lesion
Photosensitivity	++	+	+++
Alopecia	+ (diffuse)	+ (scarring)	rare
Oral ulcer	+ (painless)	non	rare
Systemic involvement	++	rare	rare
Antinuclear antibodies	anti-dsDNA, anti-Sm	negative or low titer	anti-SS-A/Ro (60-,52kDa)
LBT			
i) lesion	80-90%	80-90%	60% (DEJ&EN)
ii) non-lesion	50%	0%	25%

LBT: lupus band test; DEJ: dermoepidermal junction; DLE: discoid lupus erythematosus; EN: epidermal nuclear staining; SLE: systemic lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus.

appearance of autoantibodies and the clinical symptoms.

The antibody profiles in LE suggest that there are specific antibodies associated with certain types of cutaneous lupus. In the mouse models, anti-UVDNA antibodies are involved in the induction of skin lesions (Natali and Tan, 1973), and sera containing anti-DNA antibodies and anti-U1RNP antibodies will bind to the nuclei of living cultured keratinocyte from MRL/Mp-*+/+* mice (Furukawa et al., 1996; Furukawa, 1997). In human collagen diseases, anti-double stranded DNA and anti-Sm antibodies are disease-specific antibodies for SLE, anti-SS-A/Ro antibodies are specific for SCLE and NLE (Sontheimer et al., 1979), and anti-U1RNP antibodies are specific for mixed connective tissue disease (MCTD) (Maddison et al., 1978). Anti-SS-A/Ro and anti-U1RNP antibodies are closely associated with the development of skin lesions in autoimmune collagen diseases, and anti-SS-A/Ro antibodies can be found in the sera of SLE, DLE and other collagen diseases. In particular, anti-SS-A/Ro antibodies which recognize 60-kDa and 52-kDa proteins in the sera are strongly associated with cutaneous LE including SLE, SCLE and NLE (Table 1). The 60-kDa SS-A/Ro protein and its associated small cytoplasmic RNAs (YRNAs) colocalize in the nucleoplasm, nucleolus and cytoplasm (Farris et al., 1997). The 60-kDa SS-A/Ro protein can be considered to be the best indicator of photosensitive cutaneous lupus such as SLE, SCLE and NLE. Perhaps the best example of this photosensitivity is the UVL-induced cutaneous lesion which occurs in NLE patients, and is related to the presence of maternal anti-SS-A/Ro antibodies. As the maternal antibodies are cleared from the neonatal circulation, the NLE eruption is resolved despite repeated sun exposure. Therefore, of the many ANA, the anti-SS-A/Ro antibody, probably the 60-kDa protein, is

the best clue for investigating autoantibody-tissue damage interactions as well as LE-photosensitivity.

Changes in the autoantigen distribution on the keratinocyte surface through UVB light irradiation

The term "photosensitivity" is not entirely appropriate because: (1) a sunburn reaction is not the only factor involved in the induction of lupus lesions, (2) phototests in lupus can be variable even in similar patient populations, and (3) the UVL induction of lupus lesions is difficult, requiring multiple exposures of large areas over an extended period of time (Bennion and Norris, 1997). To better understand the mechanisms underlying photosensitivity, many studies have been performed using an *in vitro* system. Fibroblasts cultured from patients with SLE showed elevated cytotoxicity to UV irradiation (Zamansky, 1985), and a similar augmented cytotoxic susceptibility was also demonstrated in murine SLE-prone mice (Furukawa et al., 1984, 1989). However, UVL-induced phototoxicity is actually different from photosensitivity. The breakthrough was the finding that UVB irradiation induced the expression of nuclear antigens on cultured human keratinocytes (LeFeber et al., 1984). These changes in the distribution of autoantigens on the UVB-irradiated keratinocyte surface are now believed to be time-dependent.

UVB irradiation induces apoptosis of cultured keratinocytes

At earlier times (8 hours) after the delivery of UVB irradiation to cultured keratinocytes, an enrichment in lupus autoantigens such as SS-A/Ro, SS-B/La, snRNP

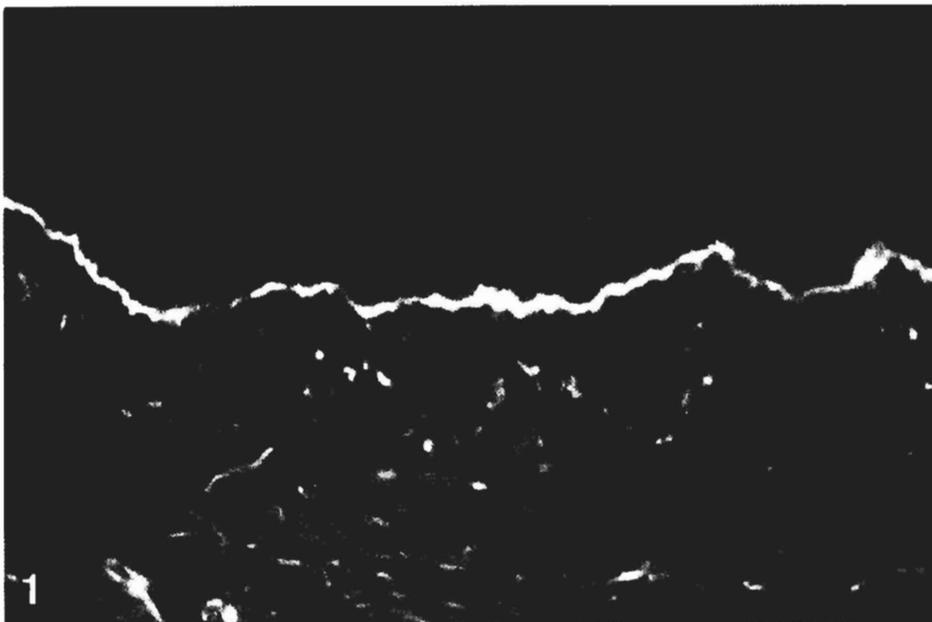


Fig. 1. Immunofluorescence photograph of the erythematous skin of a patient with SLE. IgG deposits are seen at the dermo-epidermal junction. x 100

and Sm are induced in apoptotic surface blebs on the surface of cultured keratinocytes (Casciola-Rosen et al., 1994) (Fig. 2a). This finding has led to the notion that the surface blebs of apoptotic cells are important immunogenic particles in lupus. Apoptotic cells release large amounts of oligonucleosomes (the DNA-histone chromatin constituent), and patients with lupus have high concentrations of apoptotic cells and circulating nucleosomes. Anti-nucleosome antibodies are also produced at high titers before the appearance of anti-DNA and anti-histone antibodies (Burlingame et al., 1993). At present, the nucleosomes are considered to be the primary antigens in SLE (Bach and Koutouzov, 1997), which seems to be in agreement with photosensitive cutaneous lupus.

Photosensitivity is closely associated with autoantibody binding to keratinocytes

Twenty or 24 hours after UVB irradiation, the auto-

antibodies against SS-A/Ro bind to UVB-damaged but living human keratinocytes, both *in vitro* (Fig. 2b) and *in vivo* (Fig. 3) (Furukawa et al., 1990). In addition, Golan et al. (1992) have demonstrated the enhanced membrane binding of autoantibodies to keratinocytes cultured from SLE patients after UVB/UVA irradiation. The UVB-induced surface binding of anti-SS-A/Ro antibodies was dose dependent, UVB-dependent, glycosylation-dependent, but not cell-cycle independent (Furukawa et al., 1990; Jones, 1992). Estradiol β can induce a similar binding process on cultured keratinocytes (Furukawa et al., 1988). Since these bindings were induced in cultured keratinocytes by varying extrinsic factors such as UVL, sex hormones and changes in temperature, which reflect the clinical features of cutaneous LE very well, it was concluded that the association between stress protein induction and the appearance of SS-A/Ro antigens may provide a better understanding of how environmental stimuli can promote the development of erythematous lesions in the skin (Furukawa et al., 1993).

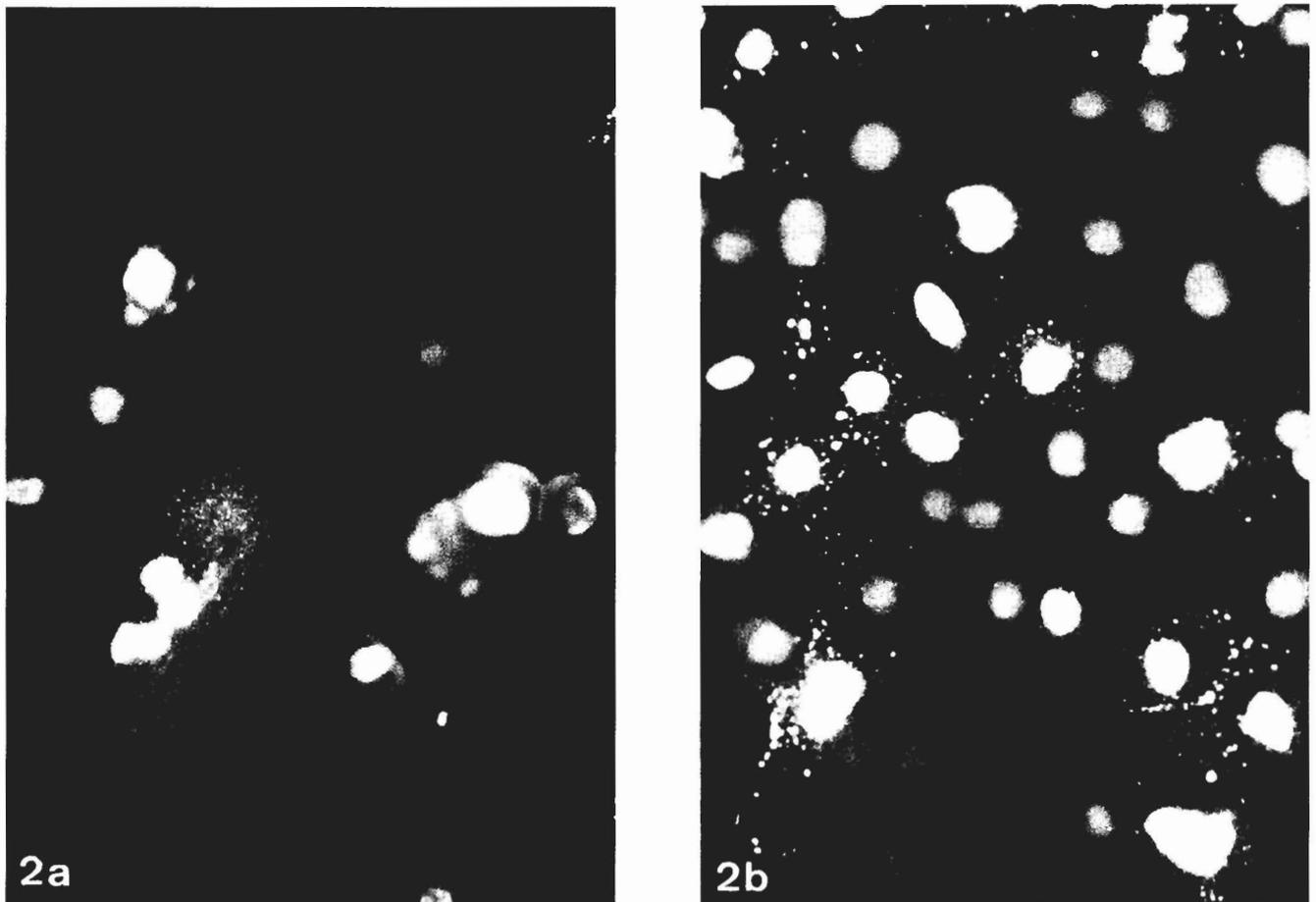


Fig. 2. Immunofluorescence photographs of cultured keratinocytes irradiated with 100 mJ/cm² of UVB light. The cells were incubated with anti-SS-A/Ro sera and fixed in cold acetone. The post-fixed specimens were then stained with FITC-labeled anti-human IgG. **a.** The apoptotic cells have surface blebs with a homogeneous binding pattern secondary to the anti-SS-A/Ro antisera. **b.** SS-A/Ro antigen expression is seen on the surface of the keratinocytes. x 200

The surface binding process of anti-SS-A/Ro antibodies on cultured keratinocytes irradiated with UVL is quantitatively different in cellular events from cytotoxicity or apoptosis, which are induced by UVB. Such binding was significantly higher in SLE and SCLE than in DLE and normal control cells. Therefore, this has become the *in vitro* phototest for monitoring the photosensitivity of cutaneous LE (Furukawa et al., 1997). The *in vitro* surface binding of sera containing anti-SS-A/Ro antibodies is a more sensitive method for detecting photosensitivity in cutaneous lupus erythematosus as compared with the *in vivo* phototest (Furukawa, 1998).

These results suggest the possibility that this process of antibody binding is an important inducer of keratinocyte damage in photosensitive cutaneous lupus erythematosus.

Table 2. Immunofluorescence findings at the cutaneous dermo-epidermal junction (DEJ) in lupus erythematosus.

IMMUNOREACTANTS	SLE (74 cases)	DLE (39 cases)	SCLE (10 cases)
IgG	42 (56.8%)	19 (48.7%)	9 (90%)
IgA	17 (23.0%)	6 (15.4%)	0
IgM	46 (62.2%)	17 (43.6%)	2 (20%)
C1q	22 (29.7%)	10 (25.6%)	0
C3	19 (25.7%)	15 (38.5%)	0
Fibrinogen	13 (17.6%)	22 (56.4%)	1 (10%)

The data are summarized from the immunofluorescence division, Department of Dermatology, School of Medicine, Hamamatsu University and Kyoto University. The number in parenthesis represents the percentage of biopsy samples which showed a positive lupus band test (DEJ and/or epidermal nuclear). DLE: discoid lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; SLE: systemic lupus erythematosus.

Anti-SS-A/Ro antibody keratinocyte cytotoxicity in cutaneous UVB-induced lupus erythematosus

Histologically, the skin lesions of cutaneous LE are characterized by the presence of basal cell damage such as liquefaction changes, lymphocyte infiltration, vasodilatation and so on. Immunoglobulins showing a binding affinity for nuclear and cytoplasmic components are also frequently observed at the DEJ of many cases, and in the cytoplasm of certain cases (Tables 1, 2). Questions arise as to why such skin tissue damage occurs, especially in photosensitive cutaneous LE. It is probable that autoantibodies, especially the anti-SS-A/Ro antibody, play an important role in the pathogenesis of the tissue injury observed in cutaneous photosensitive lupus. Several mechanisms have been proposed such as complement-mediated cellular damage (Yu et al., 1996), antibody-dependent cellular cytotoxicity (ADCC) (Furukawa et al., 1994), T-cell-mediated cytotoxicity and programmed cell death (Table 3) (Furukawa, 1998). ADCC is considered to be the best candidate, since anti-SS-A/Ro antibody binding on the surface of UVL-keratinocytes was significantly higher in cutaneous lupus.

The demonstration by Gershwin et al. (1977) of the ADCC-mediated destruction of DNA-coated targets by lupus antisera and monocyte/lymphocyte effectors raised the possibility that ADCC might be the mechanism

Table 3. Proposed mechanisms of immunologic cytotoxicity in cutaneous lupus erythematosus.

Complement-mediated cellular damage
Antibody dependent cellular cytotoxicity
T-cell mediated cytotoxicity
Programmed cell death or apoptosis

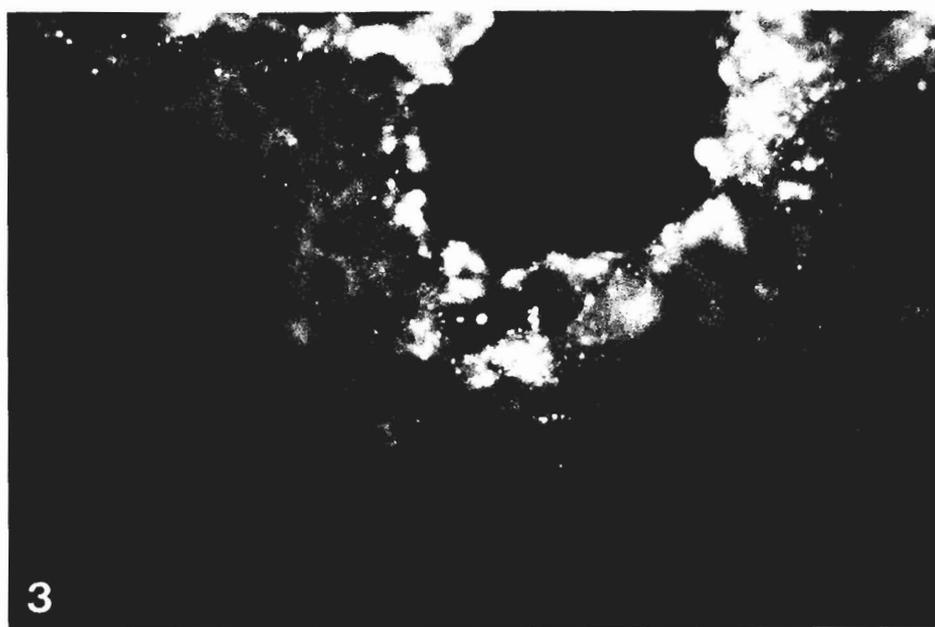


Fig. 3. Immunofluorescence photograph of a skin specimen irradiated with UVB light. The inside of the forearm of a normal control was irradiated with UVB light. Twenty-four hours later, the epidermal roofs of the erythematosus skin lesions were obtained and incubated with the anti-SS-A/Ro antisera. The specimens were then fixed in acetone and mounted in OCT compound. The cryosections were incubated with FITC-labeled anti-human IgG. Fine granular deposits are seen in the basal cell layers. x 200

Effects of antiserum probes on cultured keratinocytes from L E patients

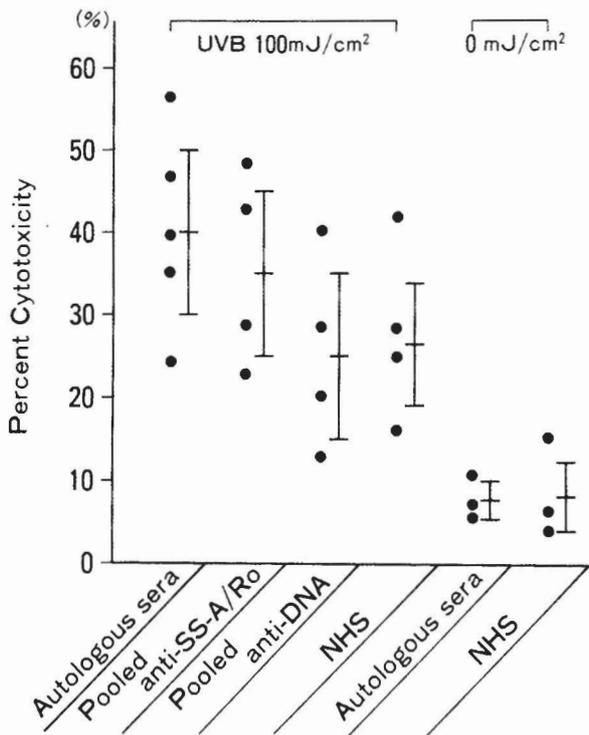


Fig. 4. Antibody-dependent keratinocyte cytotoxicity determined by AO/EB staining. Cultured keratinocytes were obtained from patients with cutaneous lupus erythematosus, and the effectors were obtained from normal healthy individuals. Each point shows the mean of three experiments performed on cultured keratinocytes from LE patients and normal controls. Each bar represents one standard deviation. The keratinocytes were irradiated with 100 mJ/cm² of UVB light, and at least 200 keratinocytes were counted in each assay.

underlying the tissue changes in LE, especially the epidermal cell destruction associated with the mononuclear infiltration in lupus skin lesions. The autoantibodies in the sera of LE patients specific for nonhistone nuclear protein antigens, such as SS-A/Ro, RNP and Sm, are capable of inducing ADCC in nuclear antigen-coated erythrocyte targets by monocyte, lymphocyte or low-density lymphocyte (K cell) effectors (Norris et al., 1984).

In the ADCC assay (Norris et al., 1988) using cultured keratinocytes obtained from cutaneous LE patients (targets), with standard sera (against SS-A/Ro or DNA), autologous sera and peripheral blood mononuclear cells from normal controls (effectors), UVB-irradiated keratinocytes from cutaneous LE patients are more susceptible to anti-SS-A/Ro antibody-dependent damage than to anti-DNA antibody-dependent damage (Fig. 4). UVB-irradiated keratinocytes from SLE patients are more susceptible to anti-SS-A/Ro antibody-

dependent damage than cells from DLE patients or controls. Furthermore, the anti-SS-A/Ro antibody shows the highest cytotoxicity against cells from SLE patients, as compared with anti-DNA antisera and normal human sera. SCLE keratinocytes are also more susceptible to anti-SS-A/Ro antibodies when compared with control keratinocytes (Furukawa et al., 1997). These experiments provide direct evidence that the sera from cutaneous LE patients, containing anti-SS-A/Ro antibodies, can directly damage self-derived keratinocytes *in vitro*.

Conclusion

UVB light induces a change in the autoantigen distribution of keratinocytes. Initially, these autoantigens are closely associated with the apoptosis process. In the next step, SS-A/Ro antigens are translocated to the nucleus and cytoplasm to the cell surface. Immunological interactions between the translocated SS-A/Ro antigens and circulating anti-SS-A/Ro antibodies may then cause the tissue injury. Anti-SS-A/Ro antibody-dependent keratinocyte damage is probably involved in the pathogenesis of cutaneous lupus, especially with respect to photosensitivity.

This finding will give new insight into the pathomechanisms underlying cutaneous LE, and will yield novel strategies for the management of these skin lesions and the subsequent development of autoimmune phenomena. It is also interesting to note that environmental factors such as UV light can induce certain interactions between the keratinocytes and the autoantibody, which may occur on the skin as well as in the internal organs, especially in systemic autoimmune diseases.

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