Photosensitivity in Rheumatic Diseases

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There have been a number of recent advances in the genetic understanding of photosensitive rheumatic diseases, especially subacute cutaneous lupus erythematosus and dermatomyositis. These advances support the concept that increased numbers of ultraviolet light–induced apoptotic cells in skin lead to a suprathreshold concentration of antigenic peptides. The current genetic data suggest that increased keratinocyte apopotosis can result from increased amounts of TNF-α that induce apoptosis due to a ultraviolet light–sensitive TNF promoter polymorphism or to decreased clearance of apototic cells due to polymorphisms associated with decreased serum levels of collectins such as C1q and mannose-binding lectin. These diseases are frequently oligogenic, and other yet to be elucidated genes will, in individual patients, lead to increased numbers of apoptotic cells associated with these cutaneous autoimmune diseases. In the presence of specific MHC class I and II genes, antigen-presenting cells initiate a primary immune response that leads to cutaneous, and likely systemic, autoimmune disease. ***Key words: dermatomyositis/lupus erythematosus/collectins/mannose binding lectin/photosensitivity/tumor necrosis factor-alpha. J Investig Dermatol Symp Proc 9:57–63, 2004***

OVERVIEW: GENETICS AND PHOTOSENSITIVE RHEUMATIC DISEASES (**FIG 1**)

Ultraviolet (UV) light is a trigger of cutaneous lesions in several autoimmune diseases. These diseases include a number of subsets of cutaneous lupus erythematosus (LE) as well as dermatomyositis (DM). Recent studies suggest that the presence of increased numbers of apoptotic cells in SCLE (subacute cutaneous LE) and DM skin relate, at least in part, to the presence of genetic polymorphisms of genes that promote UV-induced apoptosis and delay clearance of apoptotic cells. In addition, studies show that individual HLA class II genes are important in the presentation of specific antigens to antigen-presenting cells (APC, see Table 1). Clearly, more genes will be defined over time for these two diseases, but the current evidence suggests that it is often combinations of pro-apoptotic and anticlearance genes in the correct HLA setting that determine the risk of developing SCLE or DM. UV is clearly a trigger for these diseases, but it remains to be determined whether other triggers, such as infections, also play a role in genetically predisposed individuals.

A growing number of studies based on the genetics, phototesting, and serologic/pathologic testing of cutaneous photosensitive autoimmune disease patients are confirming differences between the various disease subsets. This review will focus on recent advances in our understanding of the genetics and pathogenesis of SCLE and DM, focusing on both similarities and differences between these diseases, and it will contrast these findings with those concerning other forms of photosensitive LE.

Manuscript received October 8, 2002; revised October 8, 2002; accepted for publication November 13, 2003

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Abbreviations: ADCC, antibody-dependent cellulary cytotoxicity; APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DLE, discoid lupus erythematosus; DM, dermatomyositis; HLA, human leukocyte antigen; IF, interferon; LE, lupus erythematosus; MBL, mannose-binding lectin; MHC, major histocompatibility; NK, natural killer; SBC, sunburn cell; SCLE, subacute cutaneous lupus erythematosus; TNF-α, tumor necrosis factor α; UV, ultraviolet.

DEFINITION OF PHOTOSENSITIVE AUTOIMMUNE DISEASES

The subsets of cutaneous LE that are commonly triggered by UV include subacute cutaneous LE, tumid (papulomucinous) LE, discoid LE (DLE), and systemic LE (SLE). SCLE and DLE are often clinically, histologically, and immunologically distinct (David-Bajar *et al*, 1992; Lee and Farris, 1999), as is tumid LE. SCLE and DM are similar in their histologic findings as well, but usually are distinct clinically and serologically, with anti-Ro (anti-SSA) antibodies strongly associated with SCLE (Sontheimer *et al*, 1982).

UV and phototesting Phototesting studies in cutaneous LE suggest that both UVA and UVB can trigger the photosensitive forms of LE with induction of LE lesions in 63% of SCLE cases, 72% of tumid LE cases, 60% of SLE cases, and 45% of DLE cases (Lehmann *et al*, 1990; Kuhn *et al*, 2001b). Most patients react to both UVA and UVB, although the doses of UVA used for most phototesting are well above the physiologic range. It is frequently observed that there is a delayed reaction between UV provocation and development of cutaneous LE lesions, thus making the correlation of UV exposure with exacerbation of the disease difficult to determine for many patients (Kuhn *et al*, 2001a).

Apoptosis and its role in photosensitive autoimmune diseases One of the hallmarks of cutaneous SCLE, DLE, and DM is the presence of increased numbers of apoptotic cells in lesional skin (Pablos *et al*, 1999). Recent studies suggest that UV-induced apoptosis initiates or exacerbates autoimmunity. It

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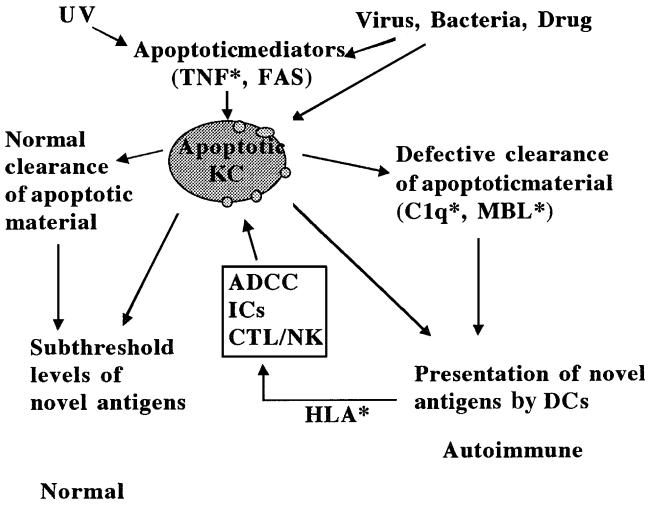

Figure 1. Model for pathogenesis of photosensitive autoimmune disease. Apoptotic cells are normally cleared by noninflammatory pathways that involve macrophages. In the presence of a number of genetic polymorphisms that lead to overexpression or underexpression of proteins involved in promoting apoptosis or impairing clearance of apoptotic cells, marked with *, various immune effector pathways that increase apoptotic death are triggered, as outlined in the box.

is likely that abnormal production or abnormal clearance of UV-induced apoptotic cells may cause a suprathreshold concentration of nontolerized antigens that is inadequately cleared by the relatively anti-inflammatory macrophage pathway. Normally, apoptotic cells are cleared very efficiently, inhibiting inflammation and inducing tolerance, in part because of anti-inflammatory cytokines (Huynh *et al*, 2002). This then allows either the apoptotic or the necrotic cells access to the MHC class I and II pathway of a population of APCs that can then, in the presence of costimulatory signals and in susceptible hosts, initiate a primary immune response, leading to autoimmunity. The exact mechanism of development of autoimmunity is unclear, and it is possible that inefficient killing and removal of autoreactive T and B cells, in the setting of specific triggers that define the autoantigen, cause expansion of the population of autoreactive T cells (Pollard, 2002).

There is evidence that UV irradiation of cultured keratinocytes causes both translocation and apoptosis of various intracellular and intranuclear antigens to small surface blebs and apoptotic bodies on the keratinocyte cell surface. These blebs and bodies are enriched in 52-kDa Ro, ribosomes, calreticulin, and phospholipid complexes (Casciola-Rosen *et al*, 1994; Casciola-Rosen and Rosen, 1997), and these lupus autoantigens can be structurally modified during apoptosis (Cacsiola-Rosen *et al*, 1995; Casciola-Rosen *et al*, 1999). Studies of T cells from cutaneous LE blood and skin suggest evidence of an antigen-driven response (Furukawa *et al*, 1996; Kita *et al*, 1998). The subsequent generation of autoantibodies, such as anti-Ro/SSA and anti-LA/SSB, recognize the cell surface of the apoptotic cell, and this is enhanced with estrogen (LeFeber *et al*, 1984; Furukawa *et al*, 1988; Furukawa *et al*, 1990). Increased autoantibody binding to keratinocytes derived from SCLE and SLE patients has been reported (Furukawa *et al*, 1999). IgG1 anti-Ro autoantibody, demonstrated in skin and blood in SCLE patients, can potentially activate both complement- and antibody-dependent cellular cytotoxicity (ADCC) (Bennion *et al*, 1990). Basal keratinocytes are more resistant to apoptosis and are targets of ADCC in SCLE (Norris *et al*, 1997). It is likely that the interaction between these autoantibodies and irradiated keratinocytes leads to cytotoxic mechanisms through ADCC (Norris *et al*, 1997; Furukawa *et al*, 1999). In addition, cytotoxic T cells can induce apoptosis independently. The strongest evidence that these autoantibodies are pathogenic comes from the neonatal equivalent of SCLE, where the neonatal skin disease resolves at the time that maternal autoantibodies are cleared (Lee and Farris, 1999).

Less is known about the relevance of distinct autoantibodies in cutaneous DM, but there is evidence of activation of complement and deposition of C5b-9 in the skin of both SCLE and DM. It is likely that lymphocyte-mediated cytotoxicity plays a role in DM and, possibly, in SCLE.

Apoptosis and UV light UV light triggers apoptosis through several mechanisms, and UVA and UVB have distinct modes of induction of the DNA damage that lead to apoptosis. Apoptosis of keratinocytes (KC), or sunburn cells, are recognized by the presence of pyknotic nuclei and shrunken and eosinophilic cytoplasm. In particular, UVB causes DNA damage through formation of thymidine dimers. It induces TNF-α via a mechanism related to DNA damage (Kock *et al*, 1990; Skov *et al*, 1997; Kibitel *et al*, 1998; Werth and Zhang, 1999). TNF-α has been shown to play an important role in UV-induced apoptosis (Schwarz *et al*, 1995; Zhuang *et al*, 1999). UVB, through DNA damage and possibly immunomodulatory factors such as prostaglandins and TNF-α, induces IL-10 (Nishigori *et al*, 1996). It also has effects on membrane and cytoplasmic targets. One example of this is UVB activation of death receptors, with direct activation of FAS (Takahashi *et al*, 2002). UVA effects are complex and involve both early and late mechanisms, some of which are mediated through reactive oxygen species and induction of pro-apoptotic FasL. There is also some activation of pyrimidine dimers with UVA, but UVA-1–induced apoptosis is not inhibited by DNA repair enzymes, suggesting potential mechanistic differences between UVA and UVA-1 (Godar, 1999; Nishigaki *et al*, 1999; Murphy *et al*, 2001; Nghiem *et al*, 2002). Both UVA and UVB induce IL-1 and IL-12, but UVB appears to selectively increase keratinocyte production of TNF-α and IL-10 (Kondo and Jimbow, 2001; Skov *et al*, 1998; Werth and Zhang, 1999; Werth *et al*, 2003). Thus, there are specific cytokines and mechanisms that account for some of the differential effects of UVA and UVB (O'Garra and Murphy, 1993). Additional mechanisms important in determining UV-induced apoptosis involve the Bcl-2 regulatory family, with control pro- and anti-apoptotic proteins located in the mitochondrial membranes. Nitric oxide protects against keratinocyte and endothelial cell UVA-induced apoptosis, possibly by induction of Bcl-2 (Suschek *et al*, 2001), but it is decreased with UVB irradiation (Yamaoka *et al*, 2000).

Because UVA and UVB can induce apoptosis, it is not surprising that both have been implicated in the induction of LE and DM skin lesions in systematic phototesting (Lehmann *et al*, 1990), although the UVA doses utilized for such testing (100 J/cm^2) tend to be higher than physiologic exposures, which are about 5 J/cm^2 per hour. Clearly, irradiation of human skin with 20 J/cm^2 is sufficient to induce significant amounts of apoptosis (**Fig 2**), and primidine dimers are induced by UVA in mice at doses of 8 J/cm^2 (Nghiem *et al*, 2002).

Fas and FasL are increased in lesional CLE skin, and Bcl-2 is decreased in the basal layer of the epidermis (Baima and Sticherling, 2001). Thus, suppression of protective Bcl-2 may be necessary prior to the Fas-induced apoptosis of basal KCs in LE skin lesions.

Although there are several pathways for apoptosis of KCs, as well as numerous anti-inflammatory regulatory molecules, studies have shown that TNF-α is a significant factor in UVB-induced apoptosis (Schwarz *et al*, 1995).

The role of pro-apoptotic genes in SCLE and DM Variant alleles associated with increased amounts of TNF-α, given the known UV induction of TNF-α and the role of TNF-α in inducing apoptosis, are prime candidates in the genetic patho-

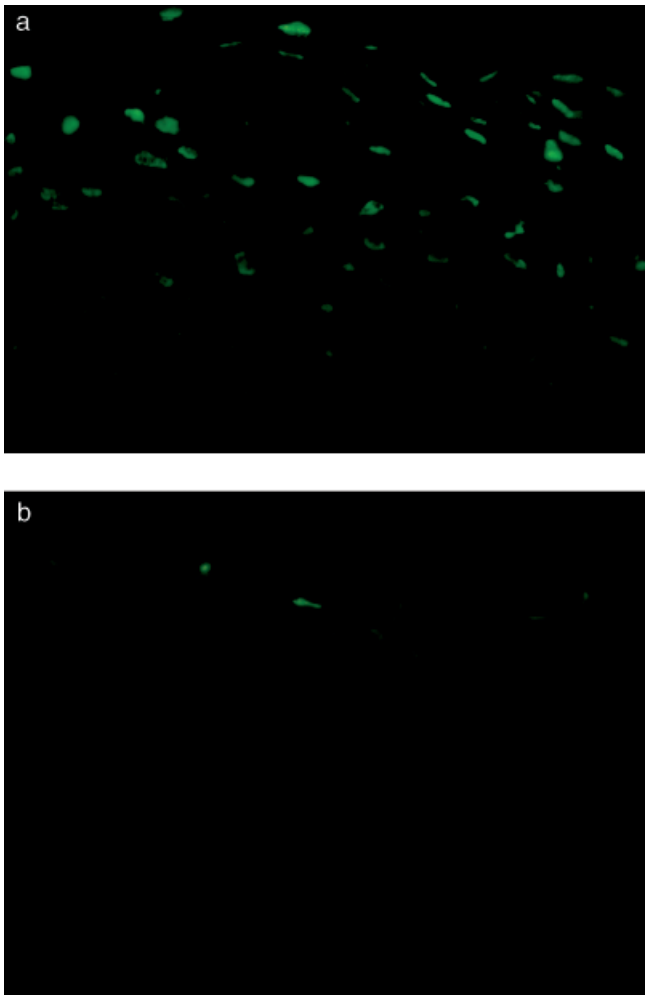

Figure 2. Skin biopsy showing TUNEL + apoptotic keratinocytes in (a) UVA-irradiated skin 48 hours after irradiation (20 J/cm^2), but not in (b) sham-irradiated normal skin.

genesis of SCLE and DM. TNF-α induces Ro and La antigen on cultured KCs, causing increased translocation or apoptosis of these cells (Dorner *et al*, 1995). The first TNF variant described within the human TNF locus was a biallelic polymorphism located at position –308 of the TNF promoter region. There is a very strong association between the uncommon TNF allele (–308 A) and the HLA-A1, -B8, and -DR3 alleles, and early studies could not demonstrate an independent association between the –308 A TNF promoter polymorphism and SLE (Wilson *et al*, 1993), probably because of the strong linkage dysequilibrium seen in Caucasians between –308 A and HLA-DR3 (Wilson *et al*, 1993). There is a strong association of HLA-DR3 and the presence of anti-SSA and anti-SSB autoantibodies in SLE patients not seen with the –308 A polymorphism alone (Wilson *et al*, 1994). Studies in African Americans with SLE, who do not exhibit linkage dysequilibrium between –308 A and HLA-DR3, determined the independent association of the –308 A promoter polymorphism with SLE (Sullivan *et al*, 1997), which has subsequently been confirmed (Rood *et al*, 2000). Reporter genes under the control of the two allelic TNF promoters demonstrated that –308 A is a much stronger transcriptional activator than the –308G wild-type promoter in a human B cell line (Wilson *et al*, 1997). More recent studies demonstrated a large increase in the –308 A promoter polymorphism in SCLE and a more modest but significant increase in both juvenile and adult DM (Pachman *et al*, 2000; Werth *et al*, 2000; Werth *et al*, 2002b). Reporter genes under the control of the two allelic TNF promoters demonstrated that –308 A is a much stronger transcriptional activator than the –308G wild-type promoter in UVB-irradiated, but not UVA-irradiated, keratinocytes, and the –308 A variant is associated with increased TNF-α production in keratinocytes (Silverberg *et al*, 1999; Werth *et al*, 2000). The initial reported association with SCLE has been subsequently confirmed in a separate cohort of SCLE patients (Millard *et al*, 2001). With a total of 52 SCLE patients in our cohort to date (51 Caucasian, 1 African American), 63% are either homozygous (15%) or heterozygous (48%) for the –308 A TNF promoter polymorphism. In the Caucasian control group, 27.7% are either homozygous (1.3%) or heterozygous (26.4%) for the –308 A TNF promoter polymorphism. No statistical difference between DLE and controls could be demonstrated, suggesting genetic differences between SCLE and DLE (Werth *et al*, 2000) and a role for increased TNF-α in the more photosensitive SCLE.

With a total of 60 DM patients in our cohort to date (55 Caucasian, 4 African American, 1 Hispanic), 45% are either homozygous (6.7%) or heterozygous (38.3%) for the –308 A TNF promoter polymorphism (Werth *et al*, 2002b). In the juvenile DM group, 48% are homozygous (26%) or heterozygous (22%), demonstrating a higher incidence of homozygosity for the overproducing polymorphism than in the adult DM group (Pachman *et al*, 2000). In addition, the disease course was longer in both TNFα promoter −308A heterozygous and homozygous juvenile DM patients and more severe and therapeutically resistant in only the −308A homozygous adult DM patients (Pachman *et al*, 2000; Werth *et al*, 2002b). Overall, these data demonstrate a highly significant statistical association of the overproducing –308A TNF promoter polymorphisms in SCLE and juvenile and adult DM.

The role of other pro-apoptotic cytokines remains to be defined in photosensitive rheumatic diseases. There is an association of three IL-10 SNPs with production of anti-Ro antibodies in SLE, as well as reports of the association of overproducing IL-10 polymorphisms with SLE (Lazarus *et al*, 1997; Gibson *et al*, 2001); however, increases in IL-10 production were not found in cutaneous LE (van der Linden *et al*, 2000).

It is of interest that UV-induced immunosuppression and tolerance induction are reversed by recombinant interleukin (IL)-12 (Schmitt *et al*, 1995; Schwarz *et al*, 1996). IL-12 suppresses IL-10 secretion from irradiated KCs and blunts the rise of plasma TNF-α that typically occurs after UV irradiation (Schmitt *et al*, 2000). Recent studies suggest that IL-12 is induced in a dose-responsive fashion by both UVA and UVB (Werth *et al*, 2003). In addition, IL-12 blocks TNF-α secretion from irradiated KCs, and this effect is mediated mostly at the level of the TNF promoter (Werth *et al*, 2003). IL-12 induces DNA repair enzymes and inhibits KC apoptosis (Schwarz *et al*, 2002). It is thus tempting to speculate that UVA-1–induced IL-12 may be responsible for inhibition of TNF-α, possibly working through DNA repair enzymes, and so accounts for the therapeutic effects of UVA-1 seen in particular with anti-Ro/SSA positive photosensitive LE patients (McGrath, 1994).

Increased UV-induced epidermal cytokines, such as TNF-α, have other ramifications in terms of potential contributions to the pathogenesis of SCLE and DM. First, UV-induced cytokines such as IL-1α and TNF-α increase keratinocyte expression of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1), which enhances the adhesion of T cells. Increases in keratinocyte and endothelial cell ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) are seen in DLE, SCLE, tumid LE, and DM (Hausmann *et al*, 1996; Kuhn *et al*, 2002). Soluble E-selectin is increased in cutaneous LE and DM (Nyberg and Stephansson, 1999; Nyberg *et al*, 1999; Kubo *et al*, 2000; Kuhn *et al*, 2002), as is soluble ICAM-1 (Kumamoto *et al*, 1997) and soluble VCAM-1.

CXCR3-activating chemokines (CXCL9, CXCL10, and CXCL11) are secreted by macrophages and activated keratinocytes, and likely bring inflammatory cells to the dermal–

epidermal junction and periadnexal areas in cutaneous LE. IFN-γ, secreted by activated T cells, macrophages, and UVA-irradiated KCs, induces not only these activating chemokines but also ICAM-1 and HLA-DR3, which are present on keratinocytes, endothelial cells, macrophages, and most infiltrating T cells (Flier *et al*, 2001). CXCR3 is expressed by both CD4+ and CD8+ dermal T cells in areas where the CXCR3-activating chemokines are present in cutaneous LE.

The role of genes related to decreased clearance of apoptotic cells in SCLE and DM The mechanisms for phagocytosis of apoptotic cells (ACs) are enormously complex, with several receptors implicated in the uptake of ACs by phagocytes. These receptors interact with their ligands on the AC either directly or through bridging proteins (Somersan and Bhardwaj, 2001). In apoptosis, there is exposure of phosphatidylserine on the outer leaflet of the plasma membrane (Hoffmann *et al*, 2001). Recent data suggest that a common pathway for apoptosis involves tethering through engagement of receptors on the phagocyte, such as CD36, αvβ3, and αvβ5 integrins, CD14, and CD68 combined with ligation of the phosphatidylserine receptor (Hoffmann *et al*, 2001). There are phosphatidylserine-independent pathways for phagocytosis, and these involve the collectins. Under noninflammatory conditions, uptake of ACs by macrophages is thought to suppress autoimmune responses through production of IL-10, TGF-β, PAF, and PGE and inhibition of proinflammatory cytokines such as TNF-α, GM-CSF, IL-12, IL-1β, and IL-8 (Somersan and Bhardwaj, 2001).

Under inflammatory conditions or when phosphatidylserine or its receptor levels are decreased, it has been proposed that other forms of clearance, such as the collectins, dominate. C1q and mannose-binding lectin (MBL) belong to a family of collectins, otherwise known as defense collagens. Collectins contain a collagen-like tail and a globular head with lectin domains. They play a role in innate immunity, and deficiences of them are associated with an increased susceptibility to infections and autoimmunity (Hansen and Holmskov, 1998; Ogden *et al*, 2001). The absence of collectins could predispose to a redirection of apototic material away from noninflammatory macrophage clearance to more proinflammatory immature dendritic cells (DC).

C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes (Korb and Ahearn, 1997). The globular head of C1q binds to apoptotic endothelial cells, and MBL binds to apoptotic Jurkat T cells (Navratil *et al*, 2001). Recent data suggest that the collagenous tail of C1q and MBL bind to macrophages through calreticulin (CRT) and CD91 on the macrophage cell surface (Ogden *et al*, 2001). C1q and MBL enhance macrophage uptake of apoptotic cells, debris, and infectious organisms through this CRT/CD91 receptor, which in turn initiates macropinocytosis and engulfment of apoptotic cells (Guan *et al*, 1994; Nepomuceno *et al*, 1997; Navratil *et al*, 2001; Ogden *et al*, 2001).

Growing evidence in SLE patients and autoimmune mouse models indicates that defects in the clearance of apoptotic cells may also be important in triggering autoimmune responses. There is abnormal clearance of apoptotic lymphocytes and fragments by macrophages in SLE (Hermann *et al*, 1998). There is impaired uptake of apoptotic cells in macrophages in germinal centers of some SLE patients (Baumann *et al*, 2002). It has been noted that C1q-deficient humans have a nearly 100% chance of developing SLE. These patients develop photosensitive eruptions (Bowness *et al*, 1994). In addition, targeted disruption of the receptor tyrosine kinase MER results in uningested apoptotic cells in the thymus, which is associated with induction of antinuclear antibodies (Scott, 2001).

Animal models with homozygous C1q deficiency develop high titers of antinuclear antibodies and glomerulonephritis, coupled with the accumulation of apoptotic bodies in the glomeruli (Botto *et al*, 1998; Taylor *et al*, 2000; Mitchell *et al*, 2002). UV irradiation studies utilizing C57BL/6, 129/Sv, and C57BL/6 × 129/Sv did not demonstrate an alteration in rate of clearance of sunburn cells after acute UV exposure, and chronic exposure did not alter the systemic disease (Pickering *et al*, 2001). More recent studies crossed these mice onto various genetic backgrounds, and it was determined that only C1q-deficient MRL/MpJ mice, but not C57BL/6-lpr/lpr or MRL/Mp-lpr/lpr strains, had acceleration of the onset and severity of renal disease and autoantibodies associated with an impairment in the phagocytic clearance of apoptotic cells (Mitchell *et al*, 2002). UV irradiation studies have not been reported in these mice.

SCLE was recently linked to a low-producing variant of the C1qA gene, and it is likely that low C1q levels permit delayed clearance of UV-induced apoptotic KCs (Racila *et al*, 2002). Probably, persistence of apoptotic and necrotic KCs leads to phagocytosis of apoptotic cells by immature DCs, which provides antigenic peptides for MHC class I and class II presentation (Rovere *et al*, 2000).

There is a parallel story developing with the role of MBL in SLE. MBL has been recognized as a basis for opsonic defects in children with immunodeficiency (Sumiya *et al*, 1991). Recent data suggest that it plays a role in increased susceptibility to infections in SLE as well as in disease activity (Sullivan *et al*, 1996; Ip *et al*, 1998; Garred *et al*, 2001; Tsutsumi *et al*, 2001), although this has not been a uniform finding (Horiuchi *et al*, 2001).

Recent studies find low-producing MBL polymorphisms highly enriched in photosensitive DM patients, but not in SCLE patients, and 53% of DM patients had more than one low-producing MBL polymorphism relative to 17% of controls ($p = 0.0002$) (Werth *et al*, 2002a). Our data show MBL-binding to apoptotic keratinocytes from UV-irradiated human skin (Rosenbaum *et al*, 2003). It is likely that deficiencies in MBL alter the ability of macrophages to clear apoptotic keratinocytes, thus allowing for persistence of apoptotic cells and debris. Suprathreshold concentrations of nontolerized antigens, in the presence of costimulatory signals, can then gain access to the MHC class I and II pathways of a population of antigen-presenting cells that initiate a primary response, leading to DM. It is unclear why MBL deficiency is associated with DM and not SCLE, but this difference probably relates to different requirements for antigen presentation in DM relative to SCLE.

C3 has been shown on sunburn cells in C1q-deficient mice, and it is likely that C3 opsonic fragments play a role in the recognition and removal of sunburn cells (SBCs) in skin (Pickering *et al*, 2001). C2 and C4 complement deficiencies, also associated with SCLE and DM, may play a role in decreased clearance of apoptotic cells.

Presentation of antigen from apoptotic cells Antigens must be taken up by antigen-presenting cells via some form of endocytic process prior to presentation to the T lymphocyte sytem. Generally MHC class I and II molecules capture peptides in the endoplasmic reticulum and endosome/lysosome system, respectively. The assembly of peptides with MHC class I is chaperoned by a number of membrane-bound (calnexin, tapsin) and soluble (calreticulin, Erp57) endoplasmic reticulum proteins. Phagocytosis of apoptotic cells by DCs usually triggers responses associated with DC maturation and antigen presentation. DCs then secrete inflammatory and immunoregulatory cytokines and chemokines; there is increased surface MHC, adhesion, and costimulatory molecules, followed by the loss of phagocytic activity and efficient antigen presentation to CD4+ T cells. The T cell clonal response to antigen can also trigger B cell autoantibody responses. Antigen uptake and MHC class I–restricted presentation is facilitated by heat shock proteins, which are upregulated by heat and UV light (reviewed in Orteu *et al*, 2001).

Dendritic cells and photosensitive autoimmune disease There is reason to believe that DCs are involved in the pathogenesis of photosensitive LE. Plasmacytoid DCs found in

lesional LE skin may be an important source of the increased IFN-α/β found in cutaneous LE lesions (Toro *et al*, 2000). In murine models, these type I IFNs can act in an autocrine manner to activate DCs, and neutralizing antibodies inhibit upregulation of costimulatory molecules, secretion of IFN-γ, and T cell stimulatory activity (Montoya *et al*, 2002).

IL-1α and TNF-α, stimulated by UVB irradiation of keratinocytes, promotes DC maturation and efficient antigen presentation (Cumberbatch *et al*, 2002). Of interest, IL-10 is inhibitory of DC maturation and is in general anti-inflammatory (Moore *et al*, 2001).

INFLAMMATORY CELLS IN PHOTOSENSITIVE AUTOIMMUNE DISEASE: THE LINK TO ANTIGEN PRESENTATION

The inflammatory cells in cutaneous LE are predominantly CD3+, with CD4+ more prevalent than CD8+ cells. There is selective expansion of Vβ8.1 CD3+ cells in skin compared to peripheral blood, consistent with an antigen-driven response (Furukawa *et al*, 1996). Sequencing of TCR clonotypes from skin also suggests an antigen-driven response (Kita *et al*, 1998). Additionally, there is evidence of active and productive antigen presentation, with the presence of B7.1 and B7.2 on antigen-presenting cells and expression of MHC class II and CD28 by infiltrating T cells in the cutaneous skin lesions of LE (Denfeld *et al*, 1997). This suggests costimulation of T cells by the B7-1 or B7-2 on APCs that interact with CD28 on T cells. T cells in cutaneous skin lesions of DM are predominantly CD4+, in contrast to the predominant CD8+ T cells found in the blood and muscle of myositis but not DM patients (Benveniste *et al*, 2001).

CXCR3 is expressed by a majority of both CD4+ and CD8+ infiltrating T cells in cutaneous LE, suggesting a functional interaction between locally produced keratinocyte and endothelial chemokines and CXCR3-expressing T cells. Other adhesion molecules such as ICAM-1 and E-selectin are likely also important.

IL-10 stimulates immunoglobulin production by B cells, and plays a major role in the pathogenesis of SLE. The role of IL-10 is less clear in photosensitive autoimmune disease, since it is known to inhibit activation and effector function of T cells, monocytes, and macrophages (Moore *et al*, 2001).

Genetics of antigen presentation The anti-Ro/SSA antibody production present in SCLE sera is influenced by the presence of specific HLA class II genes (Sontheimer *et al*, 1982; Provost and Watson, 1993). In particular, HLA-DR3 is associated with both SCLE and DM. Given the importance of TNF-α in photoinduction of autoimmunity, it is likely that the linkage dysequilibrium between the –308 A TNF promoter polymorphism and HLA-DR3 can explain some of this association. Recently it was determined that the association of the –308A TNF promoter polymorphism with HLA-DR3 is much stronger in SCLE (100%) versus DM (60%) or control (56%) (see Table 2) (Werth *et al*, 2002b). This would suggest that Ro antigen presention, enhanced because of increased apoptosis due to TNF-α, can, in the context of HLA-DR3, stimulate an autoantibody response and trigger SCLE. HLA-DR3 is seen to a lesser extent in DM patients, who show the same linkage dyequilibrium that was exhibited in Caucasian controls, thus suggesting that antigen presentation in DM is not enhanced with HLA-DR3. Recent animal experiments support the importance of HLA class II genes in terms of T cell response to autoantigens. Mice transgenic for DR2, DR3, and DQ8 showed stronger T and B cell reponses to human Ro antigen than did DQ6 mice (Paisansinsup *et al*, 2002). In addition, there is growing evidence that tissue damage during an immune response primes T and/or B lymphocytes, regardless of the specificity of the orginal insult, leading to epitope spreading. This is also determined by HLA class II genes (Paisansinsup *et al*, 2002).

Table I. Polymorphisms associated with photosensitive rheumatologic diseases:

I.	Overproduction of apoptotic cells
	–308A TNF promoter polymorphism (SCLE, DM)
II.	Decreased clearance of apoptotic cells
	C1q (SCLE)
	Mannose binding lectin (DM)
III.	Presentation of antigens from apoptotic cells
	Individual Class II HLA genes, e.g. HLA-DR3 (SCLE)

Table II. Association of HLA-DR3 and –308A TNF promoter polymorphism

TNF-308A	+	+	% TNF-308A + patients
DR3	+	–	who are also DR3 +
Controls	16%	12%	57%
Dermatomyositis	31%	20%	60%
SCLE	47%	0%	100%

It is likely that combinations of polymorphisms are at least in part responsible for the majority of SCLE and DM. Individuals who are homozygous for the –308A TNF promoter polymorphism may have enough residual antigen from apoptotic cells to trigger an immunologic response without having a clearance defect. For many patients who are heterozygous for pro-apoptotic polymorphisms, it is likely that combinations of pro-apoptotic defects with apoptotic clearance defects predispose to autoimmunity. Similarly, as seen with the MBL polymorphisms, patients often have combinations of low-producing variants that probably increase the likelihood of low MBL serum levels and decreased clearance of apoptotic cells (Werth *et al*, 2002a). Clearly, HLA genes will also play a role in antigen presentation and in determining the autoantibody response to nontolerized apoptotic antigen.

The candidate gene approach has expanded the understanding of the pathogenesis and genetic risk factors of both subacute cutaneous lupus erythematosus and dermatomyositis. The significantly increased incidence of specific genes that correlate with overproduction or decreased clearance of apototic cells, along with HLA genes involved with antigen presentation, support the concept of the relationship between genetic and environmental influences that trigger cutaneous autoimmune disease.

We thank Dr. Michele Rosenbaum for her help with Figure 2. This work is supported in part by grants from the Lupus research Institutue, National Institutes of Health (K24AR002207) and a V.A. Merit Review Grant.

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