Genetic background of cutaneous forms of lupus erythematosus: update on current evidence

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Abstract. This article reviews and updates current information on the possible genetic basis for cutaneous lupus erythematosus. The aetiology of this condition remains unknown and is believed to be multifactorial, involving genetic, environmental and retroviral factors. A genetic predisposition is probably the greatest risk factor for this condition. Individual susceptibility to lupus erythematosus may be determined by a combination of specific polymorphisms of genes encoding multiple cytokines, adhesion molecules, and cellular proteins. This condition may lead to an abnormal expression of immunoregulatory molecules and finally results in the development or exacerbation of the disease. Recently also the role of endogenous retroviral sequences in the pathogenesis of autoimmunity has been discussed.

Key words: cutaneous lupus erythematosus, gene, major histocompatibility complex, human endogenous retroviruses.


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Introduction

Lupus erythematosus (LE) is a heterogeneous connective tissue disease (CTD), which encompasses a spectrum of autoimmune diseases. It is characterized by immune deregulation with defects in immune responses, both humoral (polyclonal B-cell activation) and cellular (T-cell abnormalities). LE patients produce high titres of antinuclear autoantibodies (ANA), resulting in immune complex formation, complement fixation, and pathological tissue deposition. The disease may vary in severity from limited cutaneous lesions (cutaneous lupus erythematosus, CLE) to severe systemic disease, especially involving progressive renal damage (systemic lupus erythematosus, SLE) (PATEL, WERTH 2002).

Short characterization of LE forms

From a clinical perspective of dermatologic practice, LE-specific skin lesions are divided into 3 categories: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). ACLE has a strong association with systemic disease and identifying the type of skin involvement can prove to be a good barometer of the pattern of underlying systemic activity (CHARMAINE 2002). SCLE is a nonscarring photosensitive dermatosis. The cutaneous lesions usually take the form of psoriasiform plaques or annular polycyclic plaques. Serological abnormalities are common. About 50% of these patients will meet the criteria for classification of SLE established by the American Rheumatism Association (ARA). However, the central nervous system and kidneys are much less commonly affected in SCLE than in SLE. Discoid lupus erythematosus (DLE) is a chronic, scarring, atrophy-producing dermatosis. Localized DLE represents the most common presentation of CLE in the dermatology clinic. Serologic abnormalities are uncommon. Fewer than 5% of patients with DLE have systemic involvement. However, about 20% of patients with disseminated discoid lupus erythematosus (DDLE) go on to develop SLE (CALLEN 2002, WERTH 2002). High antinuclear antibody titres (> 1:320) and the presence of arthralgias are thought to be the risk factors that are most likely to signal transition of this form of CLE into SLE and therefore these patients should be closely monitored (TEBBE et al. 1997).

Research history of genetic background of LE

Over 100 years ago SEQUIRA (1903) described two pairs of sisters affected by CLE and suggested that it could be a familial condition. Subsequent research was aimed at CLE in monozygotic twins (STEAGALL et al. 1962). A genetic basis
for CLE was supported by a mathematic analysis of DLE incidence in the 60 s and 70 s, revealing a significantly increased prevalence of DLE in first-degree relatives of DLE probands, compared with healthy controls (Burch, Rowell 1968). Recent investigations by Lawrence et al. (1987) of DLE patients and their first-degree relatives suggested a polygenic inheritance with 44% heritability.

**Current knowledge**

Susceptibility to lupus is likely to be determined by multiple genetic regions. Several genome-wide marker scans for SLE have been performed in families with multiple affected individuals in order to identify regions of the genome that may be linked to the disease phenotype. No genome-wide searches have been performed in CLE, although DLE families with multiple affected individuals are probably sufficiently common for such an analysis to be carried out in the future. There are a number of candidate genes that may play an important role in the pathogenesis of CLE. The genes or loci for LE susceptibility are mainly situated on chromosome 6 locus 6p21.3, which includes the major histocompatibility complex genes and the long arm of chromosome 1 locus 1q23, which includes genes encoding the Fc gamma receptor II (FcγRIIA) receptor, and locus 1q31, which includes genes encoding interleukin-10 (IL-10) and Ro60 antigens. Norris (1993) proposed a probable pathogenic mechanism of photosensitive skin lesions in LE. An environmental factor, such as ultraviolet radiation (UVR), stimulates expression of nuclear antigens, including Ro on the surface of keratinocytes. Circulating anti-Ro antibodies bind the Ro antigen on the surface of keratinocytes, leading to antibody-dependent cellular cytotoxicity, resulting in the destruction of basal keratinocytes. A pathologic role of anti-Ro antibodies is evidenced by the fact that transplacental passage of maternal anti-Ro antibodies may result in development of neonatal lupus erythematosus, NLE. The antigenic target for maternal antibodies is Ro52 ribonucleoprotein – cardiac 5-HT4 serotonergic receptor that inhibits serotonin-activated L-type calcium currents (Ica). This effect could explain the pathogenesis of the cardiac rhythm disturbances observed in NLE infants (Grzybowski, Schwartz 2002).

**Human MHC genes**

Most autoimmune disorders, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or dermatomyositis (DM), are associated with certain subtypes of the human leukocyte antigen, HLA (Ridgway et al. 1999, Millard, McGregor 2001).
The human MHC (major histocompatibility complex) is a genetic region located on a segment of chromosome 6 (6p21.3) and playing an essential role in the immune system. The complete sequence and gene map of human MHC was first reported in 1999 by the MHC Sequencing Consortium. Although many of the 224 identified gene loci are still of unknown function, approximately 40% of the expressed genes have immune system functions. Historically, the MHC genes have been subdivided into three or possibly four regions: class I (telomeric), class II (centromeric), and class III. A set of more than 7 genes involved in inflammation, including 3 members of the tumour necrosis factor (TNF) superfamily, within the class III region, is sometimes specified as the class IV region (THE MHC SEQUENCING CONSORTIUM, 1999).

### Table 1. The human MHC gene organisation

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>(Class IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA B</td>
<td>HLA DQB</td>
<td>C4A, B</td>
<td>TNFα, β</td>
</tr>
<tr>
<td>HLA Cw</td>
<td>HLA DQA</td>
<td>C2</td>
<td></td>
</tr>
<tr>
<td>HLA A</td>
<td>HLA DRB</td>
<td>HSP A1A, B, L(HSP 70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA DRA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Genes of class I encode HLA A, B, Cw, those of class II encode HLA DP, DQ, DR, and those of class III encode molecules like components of complement C4A, B, C2, TNF, and heat shock proteins, HSPs (Table 1).

Several studies of class I and class II HLA in SCLE patients have identified HLA A1, B8, DR3, DQ2, DRw52 and C4null as susceptibility haplotypes for SCLE (FISCHER et al. 1994). This association was detected in SCLE, SLE and Sjögren’s syndrome patients, particularly in the presence of anti-Ro antinuclear autoantibodies. There are suggestions that MHC can control the presence or absence of the anti-Ro response and, in addition, may determine the level of this response. The highest titres of anti-Ro antibody are related to HLA DQ1 and DQ2 (HARLEY et al. 1986). The structure and common sequence variations of the Ro60 gene have already been identified (MILLARD et al. 2002). Relatively few studies have aimed to find an association between HLA and DLE. Some of these reveal an association with HLA A1, B8, DR3, B7, DR2 (BIELSA et al. 1991) while another study found no association of DLE with HLA (MILLARD et al. 1977). The class III region of the MHC includes genes for the complement components. Inherited deficiencies of the C2 and C4 components have been strongly linked to SCLE, DLE and the presence of anti-Ro. Lupus panniculitis, a special form of CLE, has also been reported in patients with partial deficiency of both C4 allotypes. These deficiencies may cause failure to clear immune complexes and apoptotic cells. Increased numbers of apoptotic cells, whether caused by increased formation or reduced clearance, lead to immunologic stimulation and fi-
nally to increased anti-Ro formation. Component C1q (encoded outside the MHC) on apoptotic cells can bind to CD91 C1q receptors on macrophages, potentially playing a role in the clearance of apoptotic cells. C1q-deficient patients tend to develop SLE with glomerulonephritis at a younger age (NOUSARI et al. 1999, LIPSKER et al. 2000, STONE et al. 2000).

TNF α and β are also encoded by MHC class III genes. The rare 308A form of the promoter is associated with increased UVB-radiation-induced TNF α production in keratinocytes in photosensitive forms of LE. The pathogenic mechanism for this is probably associated with translocation of intracellular and intranuclear antigens and their exposure to the immune system (WERTH et al. 2000).

Genes of heat shock proteins (HSPs) are located within the class III MHC. Several authors have investigated the role of HSPs in susceptibility to autoimmune and allergic diseases. HSP gene expression increases in response to stress and protects cells against stress factors, such as UV radiation, heat, and cytokines. HSPs may also be involved in the expression of Ro antigens on the surface of keratinocytes and thus may exacerbate CLE (GHOREISHI et al. 1993).

**Genes outside the MHC**

Many genetic regions outside the MHC may also be involved in susceptibility to CLE. These include genes encoding cytokines (IL-1 locus 2q13; IL-10 locus 1q31), their receptors (gamma receptor II FcγRII locus 1q23; T cell receptor TCR locus 7q23-25), adhesion molecules (ICAM-1 locus 19p13.3-p13.2; E-selectin locus 1q23-25), antioxidant enzymes (glutathione S-transferase M1 GST M1 locus 1p13), and apoptosis genes (Fas locus 10q24.1) (LAZARUS et al. 1997, BLAKEMORE et al. 1994, FRANK et al. 1990, OLLIER et al. 1996, NAKAJIMA et al. 1997). These genes most frequently demonstrate association or linkage with anti-Ro response production and photosensitivity (Table 2).

**Table 2. Genes of other genetic regions outside the MHC, which could be associated with anti-Ro response and susceptibility to CLE**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gene</th>
<th>Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td>IL-1, IL-10</td>
<td>2q131q31</td>
</tr>
<tr>
<td>Cytokine receptors</td>
<td>FcγRII</td>
<td>1q237q35</td>
</tr>
<tr>
<td></td>
<td>TCR Cβ1, Cβ2</td>
<td></td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>ICAM-1, E-selectin</td>
<td>19p13.3-p13.21q23-25</td>
</tr>
<tr>
<td>Anti-oxidant enzymes</td>
<td>GST-M1</td>
<td>1p13</td>
</tr>
<tr>
<td>Apoptosis genes</td>
<td>Fas</td>
<td>10q24.1</td>
</tr>
<tr>
<td>HERVs</td>
<td>HRES-1</td>
<td>1q42</td>
</tr>
</tbody>
</table>
Adhesion molecule ICAM-1 expression in CLE lesions is significantly increased in keratinocytes exposed to UV radiation, which induces delayed proinflammatory cytokine-mediated up-regulation of ICAM-1. Also the expression of VCAM-1 on endothelium was reported to be increased, as compared with controls, while elevated levels of E-selectin were observed in DLE patients with widespread lesions (NYBERG et al. 1999).

**Apoptosis**

Apoptosis, or programmed cell death, is characterized by cell shrinkage and nuclear condensation. Apoptosis can be induced by multiple stimuli, including UV radiation, cytokines, and cytotoxic drugs. Fas is a transmembrane glycoprotein receptor that has an intracellular death domain that initiates a cascade of events when Fas binds to the external ligand Fas L (a member of the TNF family), leading to cell death by apoptosis. Both molecules are expressed on infiltrating cells around blood vessels and hair follicles. The specific role of Fas and Fas L in CLE is still unknown. The Fas gene is located on chromosome 10q24.1 in the human genome. NAKAJIMA et al. (1997) examined Fas MvaI polymorphism in Caucasian SLE patients and found that MvaI*2 homozygosity correlates with photosensitivity. However, polymorphic Fas loci have not been detected yet in CLE.

**HERVs**

Recently, the role of retroviral sequences in the pathogenesis of autoimmunity has been discussed (URNOVITZ, MURPHY 1996, PEARL 2001, PORTIS 2002). Human endogenous retroviruses (HERVs) may have originated from exogenous retroviruses that integrated into the genome (URNOVITZ, MURPHY 1996). They constitute approximately 8% of total genomic DNA (INTERNATIONAL HUMAN GENOME SEQUENCING CONSORTIUM, 2001). While exogenous retroviruses are infectious, with a replication cycle that requires integration of proviral DNA into host cell DNA, HERVs are transmitted genetically, in a classical Mendelian fashion, as proviral DNA. Because of accumulated mutations and deletions, these elements are considered to be replication-defective but in some conditions such as UV, presence of inflammatory cytokines or demethylating agents they may be expressed spontaneously (URNOVITZ, MURPHY 1996). The hypothesis that molecular interactions between the host genome and environmental factors are critical for autoimmunity, suggests that HERVs are of particular importance (PORTIS 2002).

HERVs may lead to autoimmunity directly by encoding autoantigens, or indirectly, by affecting the expression of gene-regulating immune responses and tol-
rance (URNOVITZ, MURPHY 1996). Expression of HRES-1 and HERV-3 have been documented in SLE and antibodies to HRES-1/p28 and the env protein of HERV was detected in SLE patients and in mothers of NLE babies, respectively (BANKI et al. 1992, LI et al. 1996). Such cross-reactivity, like molecular mimicry between self-antigens and viral proteins, has been proposed as a trigger of autoimmunity in SLE (PORTIS 2002). HRES-1 (human-T-cell-lymphotropic-virus-related endogenous sequence 1), was the first HERV shown to be expressed at the protein level. In 1991 HRES-1 was mapped to human chromosome 1 at q42 (PEARL 1991). HERVs, in addition to serving as cross-reactive targets of antiviral immunity, may also play a direct role in regulating the immune response by insertional mutagenesis or cis/trans regulation of cellular genes. HERV-K10 was found to have an integration site in complement C2 gene, which may result in different expressions of C2 loci (ZHU 1992). Also, integration of a 5.3 kb Etn retrotransposon in the FasR gene locus resulted in disruption of this apoptosis pathway in lupus-prone MRL/lpr mice (WATANABE-FUKUNAGA 1992).

In a previous study, the presence of sequences homologous to the gag-pol HIV-1 region was observed in sera of patients with cutaneous forms of LE (PROKOP, KURPISZ 1996, PROKOP, KURPISZ 1998). Current studies relating to the expression of HERVs, suggest that HERVs may also be involved in the pathogenesis of these forms of LE.

Genetic predisposition to LE is probably the greatest risk factor but, as in other autoimmune diseases, the induction or exacerbation of lupus erythematosus probably results from the interplay of both genetic and environmental factors.

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