Viral infections often lead to inflammatory syndromes where arthralgias or arthritis may represent a major manifestation. Considerable evidence indicates that viruses may also be involved in pathogenesis of autoimmune rheumatic diseases. Based on the hypothesis that molecular interactions between the host genome and environmental factors are critical for autoimmunity, endogenous retroviruses (ERV) are of particular importance. They belong to the larger family of retrotransposable elements that make up as much as 40% of the human genome. ERV may have originated from exogenous retroviruses that integrated into the genome and became trapped owing to mutations of essential genes. Human ERV have generally been found to be defective proviruses. They represent a large reservoir of viral genes that may be activated by mutations caused by radiation or chemicals, or recombination with exogenous retroviruses. While exogenous retroviruses are infectious, with a replication cycle that requires integration of proviral DNA into host cell DNA, ERV are transmitted genetically in a classical mendelian fashion through the germline as proviral DNA. ERV may lead to autoimmunity directly, by encoding autoantigens, or indirectly, by affecting the expression of genes regulating immune responses and tolerance. Expression and autoantigenicity of HERV-1 and ERV-3 have been documented in SLE (Table 1). HERV-1, human T cell lymphotropic virus related endogenous sequence 1, was the first human ERV shown to be expressed on the protein level. It encodes a 28 kDa nuclear autoantigen, HERV-1/p28, which is expressed in a tissue-specific manner. Antibodies to HERV-1/p28 were detected in 21–50% of patients with systemic lupus erythematosus (SLE) and overlap syndromes in various laboratories. Antibodies to the env protein of ERV-3 were reported in patients with SLE, with the highest prevalence in mothers of babies with complete heart block. ERV, which are expressed on the protein level, are likely targets of cross-reactivity for virally induced immune responses. Such cross-reactivity, i.e., molecular mimicry between self-antigens and viral proteins, has been proposed as a trigger of autoimmunity.

In this issue, Ogasawara, et al report that transcription of HERV-E, previously termed 4-1, is increased in patients with SLE. As stated by the authors, it is presently unclear whether overexpression of HERV-E is involved in disease pathogenesis or represents a consequence of lymphocyte activation. Medstrand, et al readily detected HERV-E gag-specific RNA by reverse transcriptase mediated polymerase chain reaction (RT-PCR) in peripheral blood mononuclear cells of healthy donors. Thus, the amount, precise sequence, and chromosomal origin of lupus-specific HERV-E transcripts require further studies. HERV-E RNA was also noted in normal skin and keratinocyte cell lines. Transcription of ERV family members HERV-K, HERV-L, and ERV-9 was increased in ultraviolet B irradiated skin and skin biopsies of lupus patients. While not shown, 5-azacytidine (5-AZA), a demethylating agent, was found to enhance expression of 4-1 RNA in normal lymphocytes. This mechanism is particularly interesting with regard to induction of T cell autoreactivity by 5-AZA and impaired DNA methylation in T cells of patients with SLE. Demethylation of DNA plays an important role in toxicity of hydralazine and other lupus-inducing drugs. Antibodies to a recombinant 4-1 gagp30 protein were also reported in patients with SLE. There are at least 85 copies of HERV-E/4-1 per haploid genome scattered on 12 different chromosomes. All isolates of HERV-E are either truncated or contain multiple stop codons in their open reading frames, thus rendering them incapable of encoding proteins.
Figure 1. Pathogenicity of ERV in autoimmunity. As an example, LTR/promoter and open reading frames p28 and p15 of HRES-1 are shown. The LTR contains TATA box, poly-adenylation (polyA) site, histidine tRNA primer-binding site (PBS), an HIV-1 trans-activation region (TAR), and inverted repeats (IR) at typical locations. Transcription from the ERV LTR may be stimulated by trans-acting factors, e.g., tat of HIV-1. ERV proteins may interfere with assembly or binding of virions to cell surface receptors, affecting replication, infectivity, and pathogenicity of exogenous viruses. Immune responses triggered by viral antigens may recognize similar ERV encoded proteins, leading to autoimmunity. *Approximate location of polymorphic HindIII site in the HRES-1 LTR.

Table 1. Molecular mimicry between viral proteins and autoantigens in patients with SLE.

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>Prevalence, %†</th>
<th>Viral Protein</th>
<th>Virus</th>
<th>Reference</th>
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<tbody>
<tr>
<td>70k/U1 snRNP</td>
<td>30</td>
<td>gag</td>
<td>MoMLV, HRES-1</td>
<td>11, 41</td>
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<tr>
<td>HRES-1</td>
<td>21–52</td>
<td>gag,p24</td>
<td>HTLV-1</td>
<td>9–13</td>
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<tr>
<td>La</td>
<td>15</td>
<td>gag</td>
<td>FSV</td>
<td>42</td>
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<tr>
<td>Sm B/B′</td>
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<td>gag,p24</td>
<td>HIV-1</td>
<td>43</td>
</tr>
<tr>
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<td>30</td>
<td>ICP4</td>
<td>HHV-1</td>
<td>44</td>
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<tr>
<td>Sm D</td>
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<td>EBNA-1</td>
<td>EBV</td>
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<tr>
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<td>EBNA-1</td>
<td>EBV</td>
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<td>ERV-3</td>
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<td>env</td>
<td>MoMLV</td>
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<td>HERV-E</td>
<td>48.3</td>
<td>gag,p30</td>
<td>MoMLV</td>
<td>22</td>
</tr>
</tbody>
</table>

† Prevalence of antibodies in patients with SLE.
recombinant antigen was generated by correcting several stop codons in a genomic 4-1 sequence. Existence of a native 4-1 gagp protein has not yet been reported. Therefore, the antigen responsible for triggering these autoantibodies remains to be determined.

ERV, in addition to serving as cross-reactive targets of antiviral immunity, may also have a direct role in regulating immune responses. ERV and other retrotransposon elements possess a relatively high mobility and cause immune dysregulation by insertional mutagenesis or cis or trans regulation of cellular genes. The ERV HERV-K10 was found to have an integration site in the human complement C2 gene. Variable repeats of this element may have a role in polymorphism and differential expression of C2 loci. 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. A synthetic heptadecapeptide corresponding to the transmembrane domain of the env protein conserved among many exogenous and endogenous retroviruses has immunosuppressive properties.

ERV are part of the human genome and may genetically predispose for autoimmunity. In 1991, the ERV HRES-1 was mapped to human chromosome 1 at q42. Polymorphic genotypes in the long terminal repeat (LTR)/promoter region of the HRES-1 genomic locus have been associated with SLE. Genotype I alleles appear to protect against SLE and autoreactivity to HRES-1 in Caucasian subjects. HRES-1 is centrally located at 1q42 with respect to microsatellite markers associated with susceptibility to SLE. Thus, HRES-1 or a gene in linkage disequilibrium with this genomic locus may influence autoimmunity in SLE. The HRES-1 LTR contain poly(A) runs varied from 8 to 14 bases. Increased rate of point mutations was observed in the vicinity of the poly (A) tract. These data can be related to recent observations that mismatch repair is inhibited and mutation rates are increased by 10^3 to 10^4-fold at poly(A) tracts ranging between 8 to 14 bases. Variation of the polyA tract (11 or 12 As) of the HRES-1 LTR was also noted by others. Somatic mutations were more frequent in patients with SLE (chi-square 16.88, p < 0.001). Hypermutability at the HRES-1 LTR may be influenced by a generally higher rate of somatic mutations in SLE.

The 1q42 chromosomal region has been associated with genetic instability and identified as one of the 3 most common fragile sites in the human genome. Genomic loci harboring ERV display increased chromosomal fragility. Instability at 1q42 has shown an evolutionary conservation in humans, gorillas, and chimpanzees, similar to the appearance of HRES-1 in Old World monkeys. Moreover, fragility at 1q42 can be triggered with 5-azacytidine, a demethylating agent and relative inducer of endogenous retroviral genes in chicken cells. Many ERV are transcriptionally silent; this transcriptional inactivity is associated with host directed methylation of CG sequences in the provirus. Thus, activation of ERV, like 4-1 and HRES-1, may mediate demethylation induced autoreactivity. HERVK, HERV-L, and ERV-9, all of which are activated in lupus skin and by ultraviolet B light, have several hundred copies in the genome. It is conceivable that some of these transcripts may turn out to have uninterrupted reading frames and code for proteins. Continued research on the structure, expression, and autoreactivity of ERV is likely to yield breakthroughs for understanding the pathogenesis of autoimmune diseases.

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REFERENCES


Tsao BP. Lupus susceptibility genes on human chromosome 1. Intern Rev Immunol 2000;19:319-34.


