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Endogenous retroviral pathogenesis in lupus

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Abstract

Purpose of review—Genetic and environmental factors influence the development of systemic lupus erythematosus (SLE). Endogenous retroviruses (ERVs) are proposed as a molecular link between the human genome and environmental factors, such as viruses, in lupus pathogenesis.

Recent findings—The HRES-1 human ERV encodes a 28-kD nuclear autoantigen and a 24-kD small GTP-ase, termed HRES-1/Rab4. HRES-1/p28 is a target of cross-reactive antiviral antibodies, whereas HRES-1/Rab4 regulates the surface expression of CD4 via endosome recycling. The tat gene of HIV-1 induces the expression of HRES-1/Rab4, which in turn downregulates expression of CD4 and susceptibility to reinfection by HIV-1. HRES-1/Rab4 is overexpressed in lupus T cells where it correlates with increased recycling of CD4 and CD3 and contributes to downregulation of CD3/TCRζ via lysosomal degradation. Chilblain lupus has been linked to the deficiency of 3'-5' repair exonuclease Trex1 that metabolizes DNA reverse-transcribed from ERV. Trex1 deficiency or blocked integration of ERV-encoded DNA also promotes lupus in murine models.

Summary—ERV proteins may trigger lupus through structural and functional molecular mimicry, whereas the accumulation of ERV-derived nucleic acids stimulates interferon and anti-DNA antibody production in SLE.

Keywords

endogenous retrovirus; genetics; lupus; repetitive elements; virus

Introduction

Systemic lupus erythematosus is a chronic inflammatory disease characterized by the dysfunction of T and B-lymphocytes, macrophages and dendritic cells and autoantibody production. Independent lines of evidence have implicated genetic and environmental factors in the causation of lupus [1]. Significant familial aggregation of SLE has been clearly demonstrated by epidemiologic and genome-wide association studies [2•]. However, discordance rates of SLE are as high as 70% among monozygotic twins [3], suggesting a significant role for exogenous factors. Initially, findings of virion-like tubuloreticular structures in endothelial cells and lymphocytes as well as demonstration of elevated serum

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levels of type I interferon (IFN) raised the possibility of a viral etiology in lupus [4]. An increased prevalence of the nearly ubiquitous Epstein-Barr virus (EBV) has been demonstrated in adolescent lupus patients [5], which could contribute to disease pathogenesis via B-cell activation and triggering of antinuclear antibodies [6]. Retroviruses were implicated by detection of retroviral p30 *gag* protein in renal glomeruli and serum reactivities towards p30 *gag* antigen in patients with SLE [7]. Indeed, many features of human retroviral infections caused by HTLV-I and HIV-1 resemble those of SLE, and viral proteins have profound effects on both antigen presentation and effector functions of the immune system [8]. Dysregulation of programmed cell death has been documented in HIV-infected [9] and lupus patients as well [10–12]. Similar to SLE, anemia [13], leukopenia [14], thrombocytopenia [15], polymyositis [16] and vasculitis have been widely reported in patients with AIDS [17]. Although direct virus isolation attempts from tissues of SLE patients have not been successful [18], it is possible that a (retro)virus, responsible for provoking an immune response cross-reactive with self-antigens, has been cleared from the host, so the absence of lupus-specific viral particles is not conclusive. An alternative (retro) viral etiology, that is, activation of endogenous retroviral sequences (ERS) was initially proposed by a study of the New Zealand mouse model of SLE [19]. Endogenous retroviral envelope glycoprotein, gp 70, was found in immune-complex deposits of autoimmune lupus-prone NZB/NZW mice [19]. Abnormal expression of an ERS was noted in the thymus of lupus-prone mouse strains [20,21,22•]. More recently, expression and autoantigenicity of human ERS has been demonstrated in patients with SLE [23–27].

Molecular biology of endogenous retroviruses

ERV and ERS belong to the larger family of retrotransposable elements that make up as much as 40% of the human genome (Table 1) [28]. These elements include short interspersed nucleotide elements (SINE), such as approximately 300 bp Alu repeats, middle interspersed nucleotide elements (MINE), such as approximately 1 kb trans-aldolase-associated repetitive elements (TAREs), and long interspersed nucleotide elements (LINEs), such as L1 (Table 1). Alus and TAREs can be transcribed into nonpolyadenylated RNA by RNA polymerase III [29]. LINEs are polyadenylated and transcribed by RNA polymerase II. Their reintegration is dependent on reverse transcription. Most retroelements, Alus and truncated ERVs, lack reverse transcriptase, which can be provided in-*trans* by other retroelements, such as L1 [30]. Occasionally, mRNA transcripts of functional genes can be reverse transcribed and reintegrated into the genome thus giving rise to retropseudogenes. These sequences lack introns and contain a poly-A tail at their 3’ end. As an example, the human genome contains an intronless and polyadenylated transaldolase pseudogene TALDOP1 on human chromosome 1 (Table 1) [31].

Human ERVs (HERVs) have the basic structures of infectious retroviruses with long terminal repeats (LTRs) of several hundred nucleotides flanking sequences homologous to *gag*, *pol*, and *env* genes [32]. The *gag* gene codes for inner structural core proteins, such as matrix and capsid. The *pol* gene encodes reverse transcriptase, which copies viral RNA into DNA as well as protease and integrase allowing integration of proviral DNA into the host genome. The *env* gene codes for transmembrane and outer envelop proteins the latter playing key roles in binding to cell surface receptors. Sequence homologies between the *pol*

genes have been used to assign ERVs into two classes class I similar to mammalian type C retroviruses and class II similar to mammalian type A, B, and D retroviruses and avian type C retroviruses (Table 2) [32–48]. Human ERVs are commonly designated as HERV followed by a single letter amino acid code corresponding to a tRNA. The 3' terminus of tRNA is predicted to initiate reverse transcription by annealing to an 18 nucleotide long primer-binding site (PBS) at the 5' LTR (Fig. 1) [49,50,51•,52–54]. Human ERVs have generally been found to be defective proviruses having accumulated deletions or stop codons in *gag*, *pol*, and/or *env* open reading frames (ORFs) [55].

ERVs represent a key molecular link between the host genome and infectious viral particles. ERVs may have originated from exogenous retroviruses that integrated into the genome and became trapped owing to mutations of essential genes [32]. They constitute a large reservoir of viral genes that may be activated by mutations caused by radiation or chemicals, or recombination with exogenous retroviruses. Although exogenous retroviruses are infectious, with a replication cycle, which requires integration of proviral DNA into host cell DNA, ERVs are transmitted genetically in a classical mendelian fashion through the germline as proviral DNA. Expression of ERVs can influence the outcome of infections in different ways both beneficial and detrimental to the host [32]. These include provision of genes for recombination with exogenous viruses, interference with virion assembly, blocking cellular receptors for viral entry, and modulation of immune responses to exogenous viruses (Fig. 1).

Although expression of murine ERV can lead to production of infectious virus and cause viremia, no production of infections virion has been documented by human ERVs. The HERV-K class of human ERV may be most potent in terms of its ability to form virions [56,57]. Human ERVs show a characteristic pattern of tissue-specific expression. Most ERVs are expressed in the placenta, teratocarcinomas, and other malignant tissues. Several ERV are expressed in normal peripheral blood lymphocytes [58–60], salivary gland [25], breast [61], and keratinocytes [62].

High copy number of most ERV families makes it difficult to distinguish which members of a group are expressed. Although no single provirus with intact LTRs and uninterrupted *gag*, *pol*, and *env* ORFs have been identified, the HERV-K ERV, as a family, has been shown to encode gag [63], reverse transcriptase [64], integrase [65], and rev proteins [56,66]. The HERV-K rev protein, encoded by the LTR region, is functionally analogous to the HIV-1 rev and HTLV-I/II rex proteins. HERV-K rev binds to both the nuclear export factor Crm1 and to a cis-acting viral RNA to activate nuclear export of unspliced RNAs [66]. Alternatively, the HRES-1 LTR is transactivated by HIV-1 *tat*, suggesting a potential interaction between these exogeneous and endogenous retroviruses [50].

Mechanisms of endogenous retroviral involvement in autoimmunity

ERSs may lead to autoimmunity directly, by encoding autoantigens, or indirectly, by affecting the expression of genes regulating immune responses and tolerance [8]. Direct autoantigenicity of HRES-1 and ERV-3 has been documented in SLE. ERS, if expressed, are likely targets of cross-reactivity for virally induced immune responses. Such cross-reactivity,

that is, molecular mimicry between self antigens and viral proteins has been proposed as a trigger of autoimmunity [67,68].

In addition to serving as cross-reactive targets of antiviral immunity, ERS may also have a direct role in regulating immune responses [8]. ERS and other retrotransposable elements possess a relatively high mobility and may cause immune dysregulation by insertional mutagenesis or cis or transregulation of cellular genes [69]. HERV-K10 has an integration site within the complement C2 gene [70]. Variable repeats of this element may have a role in C2 expression. Integration of a 5.3kb ETn retrotransposon in the FasR gene locus resulted in dysruption of this apoptosis pathway in lupus prone MRL/lpr mice [71,72]. The *tat* gene of HIV-1 enhances expression of the HRES-1/Rab4 ERV protein, which in turn inhibits recycling of CD4 antigen receptor and thus infection by HIV-1 [50].

Molecular mimicry between endogenous retroviruses and infectious viruses

Immunological cross-reactivity between antigens of infectious viruses and self-proteins have long been documented (Table 3) [73–81]. However, proving a causal role of the implicated viruses has proven challenging. EBV shows cross-reactivity to several lupus autoantigens [82,83] and appears to infect lupus patients earlier than control donors [5], yet its nearly ubiquitous presence in the normal adult population makes it difficult to prove a causal role in SLE. Nevertheless, EBV remains an attractive candidate both as an initiator of autoreactivity and stimulator of B-cell survival. Other viruses with strong cross-reactivity to self-antigens, particularly the human retroviruses with homology to ERV-encoded antigens (Table 3), are also difficult to implicate in disease pathogenesis, as these viruses rarely infect patients with SLE. Along this line, relatedness and cross-reactivity to HTLV-I and HIV 1 gag antigens have been demonstrated [23,49]. However, HIV or HTLV-I provirus was absent in genomic DNA of lupus patients; thus, they could not have initiated immunoreactivity to HRES-1/ p28 [23]. Comprehensive epitope mapping with 44 15 amino acid long peptides overlapping the entire protein HRES-1/p28 by 10 amino acids with antibodies of 16 HRES-1/p28 Western blot-seropositive SLE patients identified three immunodominant epitopes within residues 41–55, 121–13, and 156–170. Two newly identified immunodominant epitopes in peptides 41–55 and 156– 170 showed significant homology to antigens of viruses commonly infecting humans [74]. The immunodominant HRES-1/p28 epitopes and viral peptides were synthesized on the same cellulose membrane and tested in parallel for binding by 16 HRES-1/p28 Western blot-reactive lupus sera. The highest prevalence of cross-reactivity was found with a ORF2a peptide of the newly discovered TT virus; 14/16 (87.5%) of lupus sera bound to this peptide. Further, antibodies from 11 patients recognized both HRES-1/p28 peptide 41–55 and TTV ORF2a peptide. All HRES-1/p28-reactive sera recognized at least one TTV peptide. In parallel, sera of 4 HRES-1/p28-seronegative lupus patients and four healthy donors failed to bind to the TTV peptides [74].

TT virus (TTV) is a recently discovered single-stranded circular DNA virus that has not been causally associated with any disease [84]. TT virus was originally named after the initials of first patient TT, then, transfusion-transmitted, and recently renamed ‘torque teno’

virus [85]. Due to the high degree of genomic variability of the putative-coding regions [86] and difficulties in expression of full-length TTV protein for antibody testing [87,88], the diagnosis of TTV infection has been dependent on PCR detection of viral DNA using primers specific for the noncoding regions [89]. TTV DNA was detected in 120/ 211 SLE patients and 66/199 healthy control donors ($P < 0.0001$). TTV DNA prevalence was also increased in SLE patients relative to rheumatoid arthritis (RA) patients (23/91; $P < 0.0001$). The prevalence of TTV DNA was increased in lupus patients (80/121) with respect to their first degree healthy relatives (40/78; $P = 0.0184$) and the prevalence of TTVDNA was also increased in first degree healthy relatives of lupus patients (40/78) with respect to unrelated healthy donors (66/199; $P = 0.0026$). Sera of all TTV PCR-positive patients recognized at least one TTV-derived peptide. HRES-1/p28 Western blot reactivity was observed in 12/23 TTV PCR-negative donors and 43/58 TTV PCR-positive lupus donors ($P < 0.0281$). In addition, TTV cross-reactive lupus sera showed high-binding affinity to HRES-1/p28 peptide 121–135 (DRRREGPDRSPRQPP) harboring three consecutive highly charged amino acids (RRE). This RRE triplet is repeated three times in the retroviral gag-like region of 70K U1 snRNP lupus autoantigen and represent cross-reactive epitopes between the two proteins [24].

HRES-1/p28 residues 41–55 (PRHRHPQDPRSPGPA) contain epitopes cross-reactive with EBV-LF3 and EBNA-3C antigens [74]. Coinfection of malignant B cells by EBV and TTV has recently been documented in non-Hodgkin lymphomas and diffuse large B-cell lymphoma [90]. Expression of HRES-1/p28 is enhanced in EBV-transformed B cells [8]. These observations suggest that cooperativity between EBV and TTV may contribute to autoantigenicity of HRES-1. Thus, coinfection with EBV and TTV and molecular mimicry with immunodominant HRES-1/p28 epitopes may mediate epitope spreading to self antigens such as the 70kD U1snRNP, and, thus, contribute to formation of antinuclear autoantibodies in SLE.

Immunomodulation by endogenous retroviruses

In addition to providing cross-reactive targets of antiviral immunity, ERV may also have a direct role in regulating immune responses. Changes in production of cytokines similar to those in patients with SLE, a shift from a Th1 to a Th2-type cytokine profile, have been described as a result of HIV-1 infection [91]. A synthetic heptadecapeptide (CKS-17) corresponding to the transmembrane domain of the *env* protein conserved among many exogenous and endogenous retroviruses has potent immunosuppressive properties [92], possibly via suppression of Th1 type cytokine production [93]. The *env* protein of HERV-W, also called syncytin [40], stimulates expression of the type D mammalian retrovirus receptor in placenta [94]. HERV-W *env* can function as an envelope protein, form pseudotypes with human immunodeficiency virus type 1 (HIV-1) virions and confer tropism for CD4-negative cells [95]. HERV-W *env* may also act as a superantigen, causing Vβ16-specific T-cell expansions [96]. In turn, ERV expression may be induced by environmental signals and activation of the immune system. Interleukin 1 (IL-1) induces expression of xenotropic ERV in pancreatic β cells of NOD mice susceptible to type 1 diabetes [97]. IL-1 and tumor necrosis factor a (TNFα) stimulate while interferon γ (IFN-γ) inhibits transcription of HERV-R in human vascular endothelial cells [98]. IFN-α induces expression of HERV-

K18.1 *env*, which acting as a superantigen causes Vβ7-specific [99] or Vβ13-specific T-cell expansions [100]. Steroids have long been known to induce expression and virion formation from ERV in the mouse [101]. Promoter of HERV-K can be induced by treatment with estradiol and progesteron [102]. Unlike related mouse mammary tumor viruses, HERV-K is not sensitive to stimulation by dexamethasone. Expression of RRHERV-I [43] and HERV-R is enhanced by retinoic acid [103]. HERV-R can also be induced by vitamin D3, IFN-γ, and phorbol esters [103]. Transcription of ERV family members HERV-K, HERV-L, and ERV-9 was increased in UVB-irradiated skin and skin biopsies of lupus patients [62]. Expression of HRES-1/Rab4 is enhanced by the tat gene of HIV through transactivation of the HRES-1 LTR [50]. In turn, HRES-1/Rab4 regulates expression of CD4, the cellular receptor of HIV, via endocytic recycling. Overexpression of HRES-1/Rab4 contributes to downregulation of CD4 and CD3/ TCRζ via lysosomal degradation in lupus T cells [51•] (Fig. 1).

HRES-1/Rab4 regulates HIV infection via recycling of CD4

Several ORFs have been identified both in the sense and antisense strands of HRES-1. The 6kb ‘sense’ transcript encodes a 28kD nuclear protein, HRES-1/p28, which is expressed in T-cell lines, placenta, and epithelial cells but not in PBL [23,25,49]. The antisense strand of the HRES-1 locus encodes a 2986 base long cDNA (Genbank accession number: AY585832) with considerable homology to the 735 base long Rab4a gene (Genbank accession number: M28211.gb_pr1), which was termed HRES-1/Rab4 [50]. HRES-1/Rab4 codes for five additional amino acids and two discordant residues, 163 (D→N) and 209 (T→A) [50]. As the HRES-1 is a single copy sequence in the haploid genome [104], the previously identified Rab4a may correspond to an alternative translation product of the polymorphic HRES-1/Rab4 genomic locus. HRES-1 was previously mapped to human chromosome 1q42 [104]. All eight coding exons of the HRES-1/Rab4 cDNA were localized within contig NT 031728.1 mapped to the 1q42 genomic locus [50]. Bidirectional transcription has been previously documented at several genomic loci [105,106], including another ERS, HERV-H [107] and the 1q42 locus harboring HRES-1 [108].

The transcription start site of HRES-1/Rab4 was mapped to HRES-1 position 1611 [50]. HRES-1 nucleotides 2151–1606 harbor the HRES-1/Rab4 promoter. The HRES-1 LTR enhanced this promoter activity in HeLa cells transfected with HIV-1 tat whereas it diminished promoter activity in control HeLa cells. Thus, HIV tat can increase expression of HRES-1/Rab4 via *trans*-activation of HRES-1 LTR [50]. Along thus line, HRES-1/ Rab4 protein levels are elevated in HeLa-tat, Jurkat-tat, and HIV-infected human PBL and CD4 T cells. Interestingly, higher expression levels of HRES-1/Rab4 abrogated production of HIV-1 gag p24 [50]. As Rab4a has been shown to regulate recycling of early endosomes carrying the TFR in epithelial cells [109] or GLUT4 in adipocytes [110], we examined whether the impact of HRES-1/Rab4 on HIV infection was mediated via recycling and expression of surface receptors. Expression of CD4 antigen was markedly reduced on the surface of cells over-producing HRES-1/Rab4. By contrast, surface expression of CD4 was enhanced by dominant-negative HRES-1/Rab4^{S27N}. As controls, HIV coreceptor fusin/CXCR4 and CD45RO were not influenced by HRES-1/ Rab4. Coordinate suppression by HRES-1/Rab4 and upregulation by HRES-1/Rab4^{S27N} indicated a specific role for HRES-1/Rab4 in regulation of CD4 expression [50].

CD4 undergoes protein kinase C (PKC)-mediated endocytosis following T-cell activation [111]. Thus, CD4 internalization was induced by activation of PKC with the phorbol ester PDBu (100 nmol/l) for 1h at 37°C. Surface expression and recycling of CD4 was profoundly reduced in cells overexpressing HRES-1/Rab4, whereas baseline expression and recycling of CD4 was markedly enhanced by HRES-1/Rab4^{S27N} [50]. Following PDBu-induced internalization, CD4 colocalized with intracellular HRES-1/Rab4 [50]. CD4 recycled to the membrane of control and HRES-1/Rab4^{S27N}-expressing cells and displayed a uniform ring pattern. CD4 failed to evenly recycle to the cell membrane and remained confined to discrete foci in cells overproducing HRES-1/Rab4. Interestingly, lysosomal inhibitors chloroquine and NH_4Cl normalized CD4 levels diminished by HRES-1/Rab4. The abrogation of CD4 expression by HRES-1/ Rab4 resulted from inhibition of endocytic recycling and targeting of CD4 for lysosomal degradation (Fig. 1) [50].

HRES-1/Rab4 overexpression inhibits endocytic recycling and promotes the lysosomal degradation of CD4 and CD3/TCRζ in lupus T cells

The role of receptor recycling and endosomal trafficking in the immune system is largely unknown, although its likely to be significant based on a few established models. A dominant-negative form of Rab4, Rab4N121I, inhibited antigen-presentation by a B-cell line to a T-cell hybridoma [112]. In T cells, CD3-induced Ca^{2+} fluxing and proliferation are enhanced in transgenic mice expressing dominant-negative Rab5 [113]. Rab27, which is involved in granule exocytosis [114], is over-expressed three-fold in effector memory T cells [115]. Patients with Griscelli syndrome and *ashen* mice exhibit albinism and hemophagocytosis due to macrophage and T-cell dysfunction. They carry inactivating mutations of Rab27 resulting in impaired melanosome transport melanocytes and defective T-cell cytotoxicity due to blocked cytotoxic granule exocytosis [114,116].

Adaptive immune responses by T lymphocytes are mediated by interaction of the T-cell receptor (TCR) with a specific peptide/major histocompatibility antigen complex on the antigen-presenting cell. The outcome of TCR engagement depends on concomitant signaling through the CD4 or CD8 coreceptor and costimulatory molecules (CD8, CD28, CD40L, LFA-1, CD2) and cytokines [117]. Intracellular signal transduction is mediated via protein tyrosine kinases (Lck, Syk) and phosphatases (CD45, SHP-1, phospholipase Cg1 (PLCg1) leading to cleavage of phosphatidylinositol diphosphate (PIP_2), and Ca^{2+} mobilization. Then, a secondary cascade of kinases, protein kinase C (PKC) and A (PKA) activate transcription factors, NFAT, NFκB, AP-1, JNK, ERK and initiate cell proliferation and cytokine production [118].

Communication between TCR engagement by the peptide MHC complex and the intracellular machinery occurs via the TCR-associated CD3 cell chains. Each CD3 cell chain contains immunereceptor tyrosine-based activation motifs (ITAMs) one each in γ, δ, and ε and three in ζ. Phosphorylation of ITAM by the Src-family kinase Lck is a critical event for initiating TCR signaling [118,119]. It has become increasingly clear the macro-molecular organization of the TCR, CD4, and signaling molecules with sphingolipid-rich membrane micro-domains (lipid rafts) and formation of an immunological synapse. Abnormal-T cell

responses in SLE have been associated with alterations in composition and dynamics of the immunological synapse, which has been also referred to as the central supramolecular activation complex (SMAC) [120–123]. The central SMAC (cSMAC) harbors the TCR, adaptor proteins, CD4, and PKCθ, surrounded by a peripheral ring (pSMAC) of adhesion factors, such as LFA-1, and a distal ring (dSMAC) containing the tyrosine phoshatases CD148 and CD45 [124]. CD4 is critical for formation of the immunological synapse/SMAC. Because a portion of Lck is constitutively associated with the CD4 coreceptor within GM1 ganglioside-positive lipid rafts [125], the peptide-MHC-induced colocalization of TCR with CD4 results in an increased local concentration of Lck around the TCR [126]. The TCRζ chain and Lck levels are reduced [120] and replaced by the Fcs receptor type I γ chain and Syk in lipid rafts, which contribute to enhanced CD3-initiated Ca^{2+} fluxing [121]. The TCRζ chain binds to the TFR [127]. Although the plasma membrane-associated Lck is bound to CD4, an intracellular pool of Lck is associated with TFR-positive recycling endosomes [128,129]. On the basis of its homology to Rab4a, HRES-1/Rab4 is likely to be activated by p85-PI3K [130] and its GTP-bound active form associates with the CD2 adaptor protein [131] and the ubiquitin ligase Cbl [132], which are localized to the immunological synapse [124,133]. The recent data on direct binding of HRES-1/Rab4 to the TFR, CD4, CD2AP, and CD3/TCRζ chain strongly suggest that HRES-1/Rab4 is involved in abnormal assembly and signaling through the immunological synapse [51•]. Both the knockdown of HRES-1/Rab4 expression by siRNA and the inhibition of lysosomal function increased TCRζ levels in lupus T-cells. These observations identified HRES-1/Rab4-dependent lysosomal degradation as a novel mechanism contributing to the critical loss of TCRζ in lupus T cells [134]. Thus, the efficacy of chloroquine in treatment of SLE may be attributed, at least in part, to inhibiting lysosomal degradation of CD4 and CD3/TCRζ. Expression of HRES-1/Rab4 may also influence T-cell activation through the trafficking of corticosteroid-inducible AMPA receptors [135], which are expressed on lymphocytes [136,137]. AMPA receptors are targeted by autoantibodies associated with seizures and other central nervous system manifestations of lupus [138]. HRES-1 alleles have been associated with SLE [27,139] and HRES-1/ Rab4 appears to be a prime candidate gene for conferring disease susceptibility at the 1q42 chromosomal locus previously linked to SLE by multiple laboratories [104,140–145].

Accumulation of endogenous retroviruses-derived DNA is associated with human systemic lupus erythematosus and promotes interferon production and lupus in murine models

Induction of type I IFN by viral DNA is a principal element of antiviral defense and a potential contributor to autoimmunity if misregulated [146,147•]. Cytosolic DNA detection activates a cell-intrinsic antiviral response through a poorly defined pathway. A screen for proteins relevant to this IFN-stimulatory DNA (ISD) response identified the 3’-5’ repair exonuclease 1 (Trex1). Mutations in the human Trex1 gene are associated with Aicardi-Goutieres syndrome (AGS) and chilblain lupus [53]. Trex1 metabolizes single-stranded DNA reverse-transcribed from ERV, ERS, and other retroelements. Single-stranded DNA accumulates and stimulates IFN-α production in Trex1-deficient cells [52]. Thus, TREX-1

deficiency is identified as a novel cell-intrinsic mechanism for initiation of autoimmunity by ERS [52]. In addition to Trex-1 deficiency [52], blocked integration of ERV-encoded DNA [148] and expression of full-length ERV promote murine lupus [148].

Expression of ERV is also controlled by epigenetic mechanisms [149], primarily via methylation [150], which appears to be deficient in lupus [151]. Stimulation of B cells with anti-IgM selectively increased the methylation of the HRES-1 promoter relative to those of CD19, CD70, Pax 5, Syk [152]. This effect by anti-IgM was reversed in the presence of IL-6, which is elevated in lupus patients, possibly hinting to a global defect in methylation of ERS in SLE [152].

Conclusion

ERVs represent a key molecular link between the host genome and infectious viruses that initiate the development or flare of SLE. ERV could contribute to autoimmunity through encoding cross-reactive antigens recognized by antiviral T cells or antibodies, proteins capable of regulating immune responses, and nucleic acids stimulating the innate immune system, IFN, anti-DNA antibody, and DNA/anti-DNA immune complex production. Expression of ERV appears to be controlled by epigenetic mechanisms and degradation of ERV-derived DNA by Trex1.

Acknowledgments

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 610).

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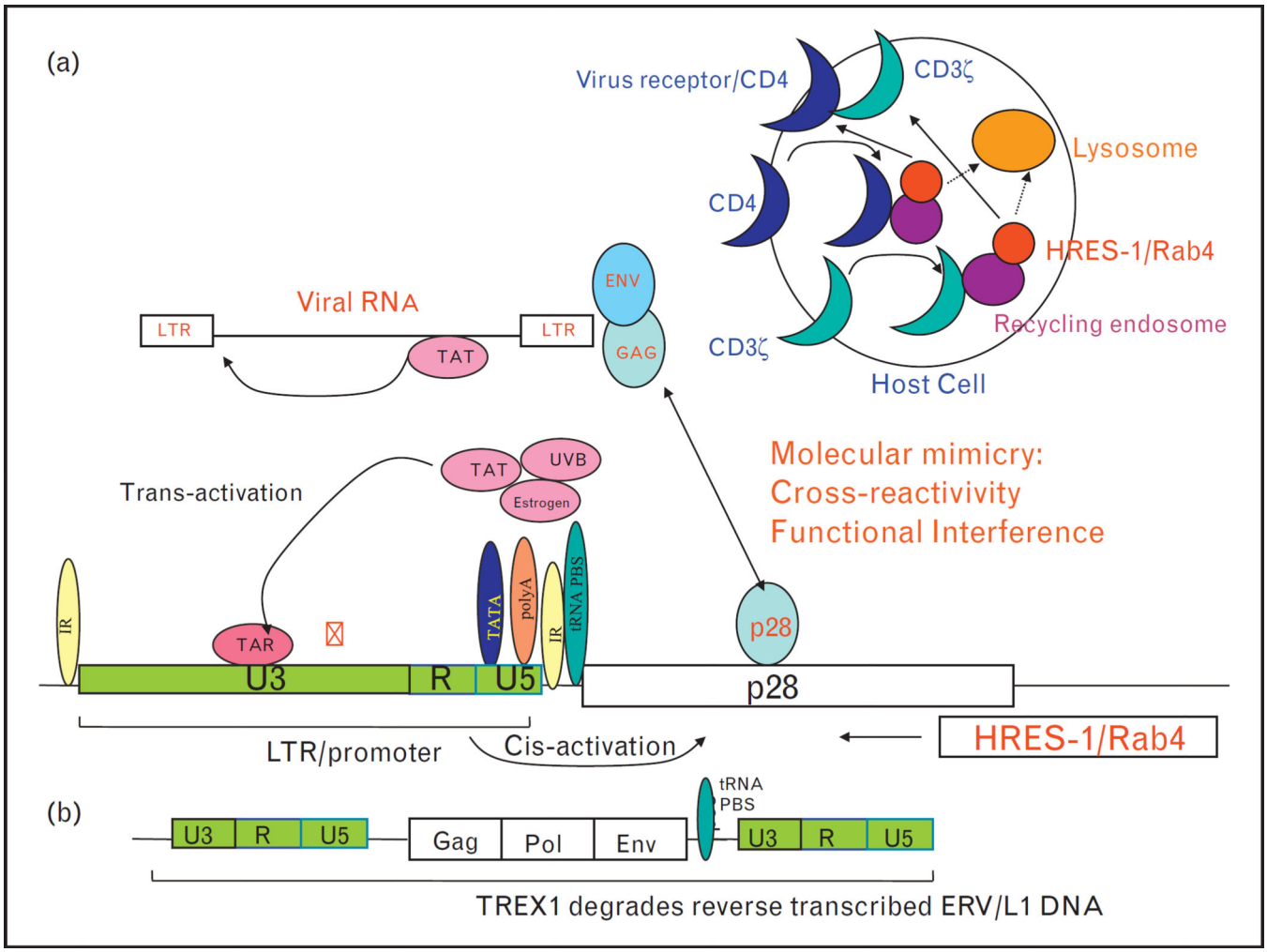

Figure 1. Schematic diagram of endogenous retrovirus-mediated mechanisms of pathogenesis in lupus

(a) Effect of ERV on autoimmunity via structural molecular mimicry, cis-activation, trans-activation, and receptor recycling. As an example, the HRES-1 LTR contains TATA box, poly-adenylation (polyA) site, tRNA primer-binding site (PBS), an HIV-1 trans-activation region (TAR), and inverted repeats (IR) at typical locations [49]. Transcription from the HRES-1 LTR may be stimulated by trans-acting factors, e.g. *tat* of HIV-1 [50]. ERV proteins may interfere with virion assembly or recycling of cell surface receptors, such as CD4 cell, thus effecting replication, infectivity, and pathogenicity of exogenous viruses [50]. HRES-1/Rab4 also regulates the recycling of the CD3/TCRζ chain [51•]. (b) ERV and L1 elements are reverse-transcribed into DNA which is in turn degraded by Trex1 [52]. Deficiency of (Trex1) has been associated with Aicardi-Goutieres syndrome (AGS) and chilblain lupus [53,54].

Table 1

Classification of retroelements in the human genome

Designation	Example	Transcription	Length	COPY number/prevalence[a]
ERV	HERV-E	RNA pol II	3–9kb	1–100
LTR retrotransposon	THE-1	RNA pol II	2.3 kb	10000
SINE	Alu	RNA pol III	300	300000
MINE	TARE	RNA pol III	~1000bp	<1000
LINE	L1	RNA pol II	6kb	10000
Retropseudogenes	TALDOP1	RNA pol II	Variable	

[a]Approximation based on hybridizations and frequency in the human genome sequence.

Table 2

Endogenous retroviruses families in the human genome

Designation	Organization	Length	Copy number[a]	Reference
Class I				
HERV-E	LTR-*gag*-*pol*-*env*-LTR	8.8 kb	35–85	[32,33]
HERV-F	LTR-*gag*-*pol*-*env*	7.1 kb	1	[34]
HERV-H	LTR-*gag*-*pol*-*env*-LTR	8.7 kb	660	[35,36]
HERV-I	LTR-*gag*-*pol*-*env*-LTR	9.0 kb	25–85	[32,36]
HERV-P	LTR-*gag*-*pol*-*env*-LTR	8.2 kb	20–100	[32,37]
HERV-R	LTR-*gag*-*pol*-*env*-LTR	9.9 kb	10–15	[36,38]
HERV-W	LTR-*gag*-*pol*-*env*-LTR	7.6 kb	15–115	[36,39,40]
ERV-1	*gag*-*pol*-*env*-LTR	3–4kb	1–15	[13,41,58]
ERV-9	LTR-*gag*-*pol*-*env*-LTR	9.6 kb	40–70	[32,36,42]
HRES-1	LTR-*gag*-Δ*pol*	6kb	1	[32]
RRHERV-I	LTR-*gag*-Δ*pol*-LTR	3.3 kb	15–20	[32,43]
S71	*gag*-Δ*pol*-*env*-LTR	5.4 kb	1–20	[32,44,45]
Class II				
HERV-K	LTR-*gag*-*pol*-*env*-LTR	9.2 kb	170	[32,36,46]
HERV-L	LTR-*gag*-*pol*-ΔLTR	6.5 kb	200–575	[36,47]
HERV.HML6	LTR-*gag*-Δ*pol*-*env*-LTR	7.5 kb	30–45	[36,48]

[a] Approximation based on hybridizations and frequency in the human genome sequence.

Table 3

Molecular mimicry between viral proteins and autoantigens in patients with systemic lupus erythematosus

Autoantigen	Prevalence[a]	Viral protein	Viral protein	Reference
70k/U1 snRNP	30%	*gag*	MoMLV, HRES-1	[24,73]
HRES-1/p28	21–52%	*gag*p24	HTLV-I	[23–27]
HRES-1/p28	21–52%	ORF2a, capsid 1	TTV	[74]
La	15%	*gag*	FSV, HERV-E	[75,76]
Sm B/B’	30%	*gag*p24	HIV-1	[77]
C/U1 snRNP	30%	ICP4	HHV-1, HERV-E	[76,78]
Sm D	36%	EBNA-1	EBV	[6]
p542	10–50%	EBNA-1	EBV	[79,80]
ERV-3	32%	*env*	MoMLV	[81]

SLE, systemic lupus erythematosus.

[a]Prevalence of antibodies in patients with SLE.