Herpes simplex virus infection as a possible modulator of autoimmune diseases facilitated by human endogenous retroviruses

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Abstract
The etiology of many autoimmune diseases such as systemic lupus erythematosus, progressive systemic sclerosis (scleroderma), and psoriasis vulgaris remains unclear. Human endogenous retroviruses (HERVs) may be involved in the development of autoimmune disease. Some exogenous infections, such as herpes simplex virus, appear to be HERV activating factors. A possible relationship will be discussed between herpes simplex virus infection and the development of selected autoimmune diseases through a suggested mechanism facilitated by HERVs.

Key words: systemic lupus erythematosus, systemic scleroderma, psoriasis vulgaris, human endogenous retrovirus, human herpes simplex virus.

Background
Herpes simplex virus (HSV) is one of the most frequently occurring infections in humans. Estimates vary greatly with respect to time and region of concern; however, the worldwide mean for HSV-2 was believed to be at about 19% in 2003 [1]. Herpes simplex virus attacks mainly epithelial cells and neurons. The clearance of dermatological symptoms does not result in its deletion from infected neurons [2]. Both the oral HSV-1 and the genital HSV-2 types enter latency, remaining in hosts for their entire lifetimes and reactivating under favorable conditions [3].

Human endogenous retroviruses (HERVs) make up about 8% of the human genome, with about 450 thousand copies in up to 200 groups and sub-groups [4, 5]. Most HERVs are far shorter than the genome of their pathogenic counterparts. The sequence similarity of HERVs to existing exogenous retroviruses seems to be the strongest argument promoting the theory of ancient prehistoric retroviral infections of germ-line cells, some of which took place even millions of years ago [6]. The vast majority of HERV sequences have been inactivated by numerous mutations throughout evolution, yet all are flanked by long terminal repeats (LTRs) and show at least minor sequence similarity to the three original genes: gag (group-associated antigen), env (envelope), excluding the HERV-L group that lacks this gene [6, 7], and pol (polymerase). Human endogenous retroviruses are not infectious, but can undergo multiple transpositions which seem to be the cause of their overwhelming number in mammalian genomes [6]. A relatively small number of HERV sequences are active in terms of transcription and translation within cells, usually generating single RNA and proteins [8].

The aim of this paper is to point out a possible, and for the moment only theoretical, relationship of HSV infection, supposedly leading to the activation of certain HERV elements and facilitation of the development of selected autoimmune disorders.

Herpes simplex virus can modulate human endogenous retroviruses expression
Herpes simplex virus types 1 and 2 are known to regulate the transactivation of LTRs in both endogenous and
exogenous retroviruses through the ICP0 protein [9]. Based on findings that viral infections activate LTRs, a significant increase was observed in HERV-W gag and env RNA levels, after infecting a neuroepithelioma cell line (SK-N-MC) with HSV-1 24 h earlier. It had been known previously that elevated levels of HERV-W and HERV-H elements are present in the cerebrospinal fluid of patients with multiple sclerosis and initial stages of schizophrenia or schizophrenic disorders [10, 11]. Hence, a question arises concerning the possible influence of HSV on these diseases. Recent findings based on in-vitro research confirm that HSV-1 induces the expression of HERV-W [11, 12]. It is believed that infection with HSV-1 or EBV can also lead to trans-activation of HERV-K elements [6]. Viral infections, including those of the Herpesviridae family, can theoretically trigger one of three effects. Firstly, they may exacerbate the existing underlying disease, therefore worsening the clinical state of the patient or increasing disease duration. Secondly, they can induce relapses. Thirdly, they might lead to a new, chronic disease [13]. A local antiviral immune response directed against HSV may lead to autoimmunologic inflammation. As a result, isolated autoantigens, such as HERV particles, may be released and spread within the organism.

**Human endogenous retroviruses influence autoimmune disorders**

Certain HERV elements are present in close proximity or even within relatively fast evolving genes such as those involved in the processes of the immunologic response. The presence of certain LTRs in the MHC gene regions correlates with the susceptibility towards autoimmunologic diseases such as type I diabetes mellitus and rheumatoid arthritis. An example of such a phenomenon is exhibited by an LTR from a HERV-K element in the gene coding for the MHC class II receptor HLA-DQ [5]. In addition, a different mechanism of the influence of HERVs on autoimmunologic disorders has been suggested, implying a role of fragmented HERV peptides in autoimmunity [6, 8]. Viral proteins may mimic host ones, generating an immunological response towards the host, a phenomenon known as antigenic mimicry [6]. Certain HERVs are also known to correlate directly with specific disorders. For example, HERV-K envelope gene transcription is at an elevated level in the vast majority of breast cancer tissues, whereas it remains normal in controls [14].

**Psoriasis vulgaris and psoriatic arthritis**

Psoriasis is one of the most common chronic inflammatory skin disorders. Genetic factors play a significant role in its development. There is also a close relationship between cutaneous and immune system manifestations [15]. Psoriasis is also one of the best known examples of cutaneous disorders where HERVs are involved. The psoriatic Koebner phenomenon might be caused by damaged keratinocytes that contain HERV particles and expose them to the immune system through a damaged basal membrane [16]. Virus-like particles, similar to murine C-type retroviruses, were found in the early 1980s in psoriatic plaques by electron microscopy. In the same study, patients with psoriatic arthritis showed serum immune complexes that contained the same antigens as the already isolated virus-resembling particles [17]. Another group of scientists found three known HERV families, namely W, K, and E, expressed in psoriatic plaques. They also discovered and characterized a completely new family related to ERV-9/HERV-W. The novel sequence includes at least two ORFs showing sequence similarity towards the retroviral gag and protease genes [15]. Furthermore, in a different study researchers found elevated HERV-W env and HERV K10 gag transcripts in patients with psoriasis vulgaris and psoriasis arthritis in comparison to healthy volunteers. They also found elevated levels of transcripts of HERV-E gag in patients with psoriasis arthritis along with the downregulation of the same sequence in psoriasis vulgaris [18]. Using immunofluorescence and immunoblot methods, Bessis et al. [19] found HERV-E envelope glycoprotein in 95% of skin samples from patients with psoriasis and atopic dermatitis, compared to only 15% of skin samples from positive healthy volunteers. Additionally, the positive signals from the control group were faint.

**Progressive systemic sclerosis (systemic scleroderma)**

Scleroderma can be divided into two major subtypes, localized cutaneous and systemic. These two types show major differences in their clinical manifestations, but share similarities such as skin sclerosis, vascular disorders and fibrosis. The etiology and pathogenesis of scleroderma are complex and multifactorial. Immunogenetics, microchimerism of fetal cells that survive within the mother, environmental, and other factors are all taken into account as possible causes or risk factors. An autoimmunologic response towards an unknown antigen of viral origin might underlie the processes of systemic scleroderma development [18, 20]. Knowledge on HERV expression and its influence on scleroderma is relatively small. There are findings claiming elevated levels of HERV-W env, HERV K10 gag, and HERV-E gag transcripts in scleroderma patients in comparison to controls [18]. Additionally, there seems to be a relation between HERVs and the classical complement pathway. The lack of C4A is closely related to a number of autoimmunologic disorders such as scleroderma. There is a copy of HERV-K, within intron 9 of the C4A coding gene, which is absent in cases of C4A deficiency [21]. Furthermore, one study emphasized apparent production of
anti-retroviral antibodies, found in plasma and tissue samples of sclerodermic patients, that suggests the influence of HERV expression in this aspect [22].

Systemic lupus erythematosus

Although the underlying cause of systemic lupus erythematosus (SLE) is unclear, retroviral factors may play a significant role in its pathogenesis [23]. The MRL/1pr murine model has revealed a functional link between the integration of a certain HERV sequence in the host’s genome and the development of SLE. Namely, an integration of HRES-1 (HTLV-1 related endogenous sequence) leads to lowered expression of Fas protein and therefore failure of autoreactive lymphocytes to undergo negative selection [24]. It has been known for years that patients with SLE produce a high titer of antibodies binding to a number of retroviral proteins, including gag and env, without a clearly stated retroviral infection [16, 20]. Systemic lupus erythematosus positive patients do produce anti-HERV antibodies. The apparent similarity between certain amino acids in HERV peptides and human autoantigens (e.g. the 70 K protein of sn-ribonucleoprotein, topoisomerase 1, and SS-B/L) suggests that the primary targets of these autoreactive antibodies are HERV particles [16, 20]. Significantly, anti-HTLV-1 antibodies may bind to endogenous retroviral proteins such as HRES-1, the HTLV-1 counterpart in the human genome. At least 52% of SLE patients evaluated produced antibodies against HRES-1, whereas only 3.6% of the control group did. Furthermore, none of the patients with AIDS or asymptomatic HIV-1 infection appeared to produce such antibodies [25]. Autoantibodies against HRES-1 can be found in a specific subgroup of patients with autoimmune disorders, primarily in patients that do not show anti-Ro and anti-La antibody production [16]. Based on the analyses of HERV influence on SLE in humans and mice, along with comparison of the natural antibodies against retroviral epitopes, molecular mimicry between HERV and gag resembling region of sn-RNP may be one of the crucial causative factors in the etiology and pathogenesis of SLE. A natural target of antiretroviral antibodies seems to be HRES-1 rather than sn-RNP. That is why the addition of HRES-1 (HTLV-1 related endogenous sequence) may be an early stage of the development of SLE, leading to a collapse of tolerance towards other autoantigens [16]. A different theory concerning the influence of HERV-K in SLE parallels that of scleroderma, as the lack of C4A complement gene, which contains the HERV-K sequence in intron 9, might also contribute to the development of SLE [21]. An apparent relationship between elevated transcript levels of HERV-E 4-1 clone and the production of SLE specific antibodies such as U1 RNP and anti-SM is noteworthy [26]. The stimulation of transcription of the HERV-E 4-1 clone might be related to inactivation of stop codons and hypomethylation within the clone [27]. The influence of epigenetic changes in the genomic DNA and their relation not only to cancerogenesis but also to autoimmunity. Such changes could also be co-responsible for the disorders of the immune system of SLE patients [28].

Conclusions

Human endogenous retroviruses particles are found in both autoimmune patients and healthy individuals. The precise role and mechanism of HERVs in diseases remains unknown. Correlations between HERV transcription levels and clinical manifestations of psoriasis, scleroderma, lupus erythematosus, and other disorders have been demonstrated.

Herpes viruses can cause elevation of certain HERV transcripts, which correlates and possibly contributes to a number of autoimmune skin diseases. However, there is still a missing logical, and scientifically confirmed, link between a direct influence of herpes, and other viruses, on autoimmune disorders through the HERV mechanism. A group of scientists is examining the possible correlations between HSV infection, altered HERV transcription levels, and autoimmune skin disorders. The situation is complicated by confusion regarding names assigned to families/groups of endogenous retroviruses as well as individual HERV loci. In addition, there is a close relationship between HERVs and exogenous retroviruses, so a reconciliation of both of their classifications would be desirable [29]. The understanding of possible interactions between HERVs and exogenous retroviruses might be facilitated in this way.

Another type of herpes virus, HHV-8, is necessary but not sufficient to produce Kaposi’s sarcoma (KS) in humans [30]. Male AIDS patients with a history of using anti-herpetic medications had a lower incidence of developing KS. One might analyze those females, the gender most likely to get SLE, who happen to be on anti-herpetic medication for a HSV infection, to ascertain if there is a lower incidence of SLE in them. If there is, the use of a relatively safe, nontoxic and inexpensive oral anti-herpes medication, such as acyclovir, might lower the incidence of SLE and/or reduce its severity in those affected.
References