YALE JOURNAL OF BIOLOGY AND MEDICINE 97 (2024), pp.521-528. doi: 10.59249/OIKF8301

MINI-REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM

Human Endogenous Retroviruses Expression in Autoimmunity

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In relation to ancient infections, a substantial number of retroviral sequences with persistent immunogenic potential were integrated within the human genome (HERVs). Under physiological conditions, coding sequences from HERVs can participate in cell/tissue homeostasis and physiological functions in an epigenetically controlled manner. However, HERV expression is susceptible to contribute to various pathologies, including autoinflammatory and autoimmune disorders, when reprogrammed by exogenous stimuli such as drugs or microbial infections. Both innate and adaptive components of the immune system can be mobilized in response to deregulated/de-repressed expression of HERV determinants and thereby, modify immune tolerance to tissue antigens. Self-directed immune responses induced/worsened by HERV expression are suspected to participate in both tissue-specific and systemic disorders. A substantial level of mechanistic investigation is needed to better delineate the impact of HERV expression in diseases in general, and in inflammation and autoimmunity in particular.

INTRODUCTION

Among its transposable elements, the human genome contains a large number of retroviral elements, up to 8% of the host DNA, acquired over time due to multiple events of retroviral infection and integration in the germline (see [1] for an overview). Many of such human endogenous retroviral elements (HERVs), that are still incompletely characterized, have been subjected to truncation and/or mutation events rendering them defective in their replication capacity relative to the parental retroviruses. However, a substantial number of HERVs do include functional regulatory sequences called long terminal repeats (LTRs) that flank structural proteins for the capsid, nucleocapsid and matrix (gag), protease (pro), reverse transcriptase, RNAse and integrase (pol), and envelope protein subunits (env) genes. HERVs belong to either γ-retrovirus (I), β-retroviruses (II), or spumaviruses (III) classes depending on their pol gene sequence. The most recently integrated HERVs belong to the so-called HERV-K(HML-2) family that represents the less modified group of HERV capable of neo-integration [2,3].

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Abbreviations: AH, autoimmune hepatitis; BCR, B cell antigen receptor; EBV, Epstein Barr virus; Env, envelope protein; Gag, polyprotein precursor of structural proteins; HERV, human endogenous retrovirus; HLA, human leukocyte antigen; IFN-I, Type I interferon; IL, Interleukin; LTR, long terminal repeat; MS, multiple sclerosis; PBMC, peripheral blood mononuclear cells; Pol, polyprotein with reverse transcriptase, RNAse and integrase activities; Pro, protease; RT, reverse transcription; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; TCR, T cell antigen receptor; TLR, toll-like receptor; TNF, tumor necrosis factor; T1D, type 1 Diabetes.

Keywords: Human endogenous retroviruses, innate and adaptive immunity, autoimmunity

Author Contributions: CV and MSB discussed and planned the outlines, CV drafted the manuscript. CV is a CNRS investigator. MSB work is supported by the National Institutes of Health (Grant RO1NS063011).

Full-length HERVs harbor a low transcription status or are kept transcriptionally silent due to epigenetic mechanisms such as modification of histones or DNA methylation yet, many HERVs remain capable of expression and even of neo-integration. Consequently, an equilibrium exists between HERV expression and the immune system under physiological condition [4,5]. Expression of HERV components can modulate the function of various genes of the host [6] and even a solitary LTR can exert promoter/enhancer function on other genes. De-repression of HERV expression can be triggered by various exogenous (microbial infections, drugs, mitogens, radiation, environmental factors) and endogenous (hormones, cytokines, aging-related processes) stimuli [7]. When neo-expressed, HERV transcripts and proteins are sensed and opposed by innate and adaptive immune responses of the host. Such immune responses can influence the overall immune reactivity to microbiota, to incoming pathogens as well as to host tissue antigens. In the latter case, the elicited immune deregulation may possibly promote or worsen autoimmune disorders. Indeed, HERV determinants can be found at lesion sites but what remains unclear in most cases is whether induced HERV expression directly contribute to the onset of disease or whether it is secondary to disease initiation and therefore, may play a rather aggravating/amplifying role. As we shall see, mechanisms put forward to account for a possible role of HERVs in autoimmune disorder pathogenesis include transcriptional activation, innate immunity activation, molecular mimicry, superantigen activity, and immune modulation. This mini-review focuses on the proposed link between HERVs and autoimmunity. Issues relative to retroelements other than HERVs (eg, long and short interspersed nuclear elements (LINE and SINE)) are not covered here.

INNATE AND ADAPTIVE IMMUNITY ACTIVATION BY HERV EXPRESSION

HERV expression may participate in promoting autoimmunity through the induction of proinflammatory mediators via the sensing of retroviral nucleic acids and proteins [8]. Replication intermediates associated with HERV expression can be detected by evolutionary conserved sensors of nucleic acids. Thus, single stranded RNA can engage Toll-like Receptor (TLR)-7/8 through the autophagy pathway, via endocytosis of assembled particles or even extracellular RNA such as that of HERV-K(HML2) [9]. DNA derived from HERV reverse transcription (RT) may also be detected by specialized innate receptors and accordingly, RT inhibitors appear capable of alleviating the immune activation associated with such expression [10-13]. Of note, double-stranded RNA generated by bidirectional transcription of HERVs can activate TLR-3 and MDA5 innate sensors [14-16]. Type I interferon (IFN-I) production can also be associated with HERV expression [12,17]. Enzymes able to restrict the replication of endogenous retrovirus via dNTPs degradation, RNA degradation or DNA product hydrolysis can limit deleterious innate immune responses and their loss of function mutation can lead to IFN-I-dependent autoreactivity [18]. Expression of HERV products, such as the HERV-K(HML2) envelope protein or HERV-W/Syncytin-1, can activate signaling pathways able to modulate inflammation and/or cell death [19-21]. Hence, the neo-expression of HERV components (nucleic acids, proteins, particles) may stimulate innate immune responses through the engagement of conserved, non-clonally distributed, receptors able to sense the presence of microbial products (ie, pattern recognition receptors). Such responses represent an inflammatory context susceptible to trigger activation of auto-specific lymphocytes that would otherwise remain silent due to tolerance mechanisms. In parallel, HERV protein expression can also activate anti-HERV adaptive immune responses by initiating antibody production and/or T cell-mediated recognition of HERV epitopes in the context of molecules of the human leukocyte antigens (HLA) complex. Both types of adaptive responses are likely to be favored by the concomitant activation of innate mechanisms through an adjuvant effect. A link between anti-HERV adaptive immune responses and auto-reactivity can be described by using the so-called mimicry hypothesis that relies on cross-reactivity, a major characteristic of clonally distributed T/B cell antigen receptors. Thus, activated HERV-specific T cells able to cross react with a structurally related tissue-specific antigen may contribute to autoreactive attack against an organ expressing that antigen. Another possible activation mode of cross-reactive T cells involves the stimulation of large subsets of T cells that share a given variable segment (Vβ) at the level of their T cell receptor (TCR) beta chain (super-antigenic activity). Finally, HERV neo-expression may disrupt immune homeostasis through deregulated transcription of genes involved in immune regulation (eg, *cis* regulation of insertional modulation of cytokine genes or complement cascade genes).

HERV EXPRESSION IN AUTOIMMUNE DISORDERS

Multiple Sclerosis

Multiple sclerosis (MS) is a multifactorial chronic autoimmune and degenerative disorder that targets the central nervous system (CNS). Genetic and environmental factors are thought to participate in autoreactive T/B lymphocyte activation and subsequent CNS parenchyma

infiltration. Consequently, focal inflammatory lesions due to neurons and oligodendrocytes immune targeting occur within the brain and spinal cord, leading to progressive neurodegeneration. The presence of retroviral particles related to the HERV-W family (named MSRV) in the cerebrospinal fluid of MS patients [22-25] pointed to a possible association between MS and HERV expression. In line with this notion, the brain of MS patients harbored elevated levels of MSRV env and pol transcripts as well as a marked expression of MSRV env protein that correlated with the magnitude of inflammation and demyelination [26]. Via its surface subunit (su), the MSRV envelope protein expressed by microglial cells and macrophages is likely to contribute to neuroinflammation through activation of innate immune pathways such as the TLR-4 associated pathway [27,28]. Interestingly, HERV-W glycoprotein syncytin-1 expression was also elevated in astrocytes and microglial cells in demyelinating MS lesions and capable of triggering the production of interleukin (IL)-1β and ROS that are toxic to oligodendrocytes [21]. It was also elevated in monocytes during disease relapses and acute infections. Peripheral blood mononuclear cells (PBMCs) expressing syncytin-1 displayed an activated phenotype. Syncytin-1/HERV-W may thus also contribute to inflammation through leukocyte activation [29]. In addition, augmented levels of serum antibody directed to envelope glycoprotein epitopes of HERV-H and HERV-W proviruses have been noticed in MS patients with active, but not stable, disease. Such levels correlated with increased expression of these proteins on monocytes and B lymphocytes [30,31]. Of note, Epstein-Barr virus (EBV) infection, whose link to MS is increasingly suspected [32], can stimulate HERV-W/Syncytin-1 and MSRV env expression in astrocytes and subsets of PBMCs [33].

Nevertheless, deciphering the exact role of HERV expression in MS pathogenesis remains a difficult task. In the case of the MSRV envelope glycoprotein [34], the humoral and cellular reactivity of MS patient samples can be difficult to recapitulate *in vitro* [35] and a humanized monoclonal antibody against MSRV-Env (IgG4 GNbAC1 or Temelimab) that blocks its binding to TLR-4 failed to significantly attenuate severe inflammation in clinical trials despite a positive effect on neurodegeneration likely due to reduced peripheral innate response to MSRV-env and diminished microglial cell activation within the CNS [36]. Moreover, additional complications arise, such as the detection of many additional HERV families in transcriptomic data from secondary progressive forms of MS [37].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is another multifactorial chronic disorder with engagement of both innate and adaptive immune responses leading to marked immune complexes deposition, organ specific lesions and systemic manifestations. Both genetic and environmental factors appear involved in a loss of self-tolerance and dysregulated immune responses to autoantigens. Among salient features of SLE are an important role for IFN-I, an altered function of regulatory T cells (Tregs), anti-nuclear autoantibodies and abnormalities in B cell development and activation. In addition, alteration in both phagocytosis and complement activation impairs the disposal of apoptotic cells thereby, causing the accumulation of self-determinants and the perpetuation of autoreactivity. Deregulation of HERV expression has been suggested in SLE pathogenesis. For instance, antibodies to the prototypic HERV HRES-1 have been detected in subsets of SLE patients [38]. In relation to this, it was found that DNA methylation directly modulates expression of HRES-1/p28 in B lymphocytes from SLE patients [39]. Interestingly, the methylation of some HERV-E/K LTR sequences was found lowered in CD4 T cells from SLE patients and, for a given sequence, this differed depending on the active versus inactive phase of the disease [40]. An increased level of HERV-E clone 4-1 gag region transcripts has been noticed in patients and in half of them, anti-gag antibodies were detected as well [41-43]. Of note, augmented expression of HERV-E clone 4-1 promotes secretion of the inflammatory cytokine IL-17 by CD4 T cells via recruitment of nuclear factor of activated T cells 1 (NFAT1) and estrogen receptor alpha [44]. Interestingly, demethylating agents able to induce HERV-E clone 4-1 gag expression in control cells could not further increase its expression in patient cells, indicating a pronounced alteration of the methylation status of this HERV in SLE [45].

Besides HERV-E clone 4-1, the HERV3-1 envelope glycoprotein was found to be targeted by a humoral response in fractions of both SLE and the juvenile form of the disease [46,47]. Antibodies directed to HERV-K(HML-2) envelope glycoprotein can also be detected in the plasma of SLE patients most likely due to expression of the HERV-K(HML-2) provirus named ERVK-7/HERV-K102. This expression, which correlated with augmented interferon stimulated gene expression, appears able to trigger neutrophil activation which is part of the innate immune activation associated with inflammation in SLE [48]. Indeed, the expression of more than 100 unique ERV *loci* is significantly increased in peripheral blood mono-nuclear cells in SLE, however, no consistent association with interferon-stimulated gene expression [49]. Finally, expression of the HERV-E LTR that influences expression of the signaling regulatory factor CD5 (HERV-CD5) lowers the activation threshold of the B cell antigen receptor (BCR) [50], likely favoring autoreactive

B cell activation.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a multifactorial chronic inflammatory disorder leading to joint destruction due to immune cell infiltration and synovial membrane attack. Disease susceptibility is markedly associated with the class II molecule HLA-DR4 whose beta chain sequence influences the presentation of arthritogenic antigenic peptides. In this instance, self-antigens post-transcriptionally modified by citrullination appear to play an important role in the activation of aggressive CD4 T cells. HERV gene expression (pol transcripts) analyzed in synovial fluid cells from RA patients identified the HERV-L-related F6 sequences as increased in frequency [51]. Among HERV transcripts abnormally augmented in RA patients PBMCs were also the HERV-K10 gag transcripts [52] as well as the HERV-K (HML-2) gag and Rec transcripts [53-56]. Moreover, serum antibodies to an env-su determinant of HERV-K were elevated in patients [57] and patients with juvenile RA showed elevated HERV-K18 expression in blood [58]. In contrast with SLE, HERV-E clone 4.1 gag expression was not increased in patient sera [59].

Type 1 Diabetes

Insulin-dependent diabetes mellitus or Type 1 Diabetes (T1D) is a complex multifactorial autoimmune disorder in which pancreatic beta cells that produce insulin are specifically targeted and destroyed by T lymphocytes. As for many autoimmune disorders, both genetic susceptibility (eg, allelic variants of HLA-DRB1, HLA-DQA1, and HLA-DQB1 class II molecules) and exposure to environmental triggers play a role in T1D pathogenesis. Both activated CD4 and CD8 T cells are involved in insulitis and to beta cell antigens recognition. Antibodies reacting to beta cell antigens are also present. A HERV-K18-related HERV (IDDMK(1,2)22) with Env-associated superantigenic activity has been suggested to play a role in T1D pathogenesis [60,61] but such a role was not supported by additional studies [62-64]. More recently, a large fraction of T1D patients studied were found to express HERV-W/MSRV env transcript in PBMCs and carry the corresponding protein in the serum. Interestingly, the env protein was expressed in pancreatic acinar cells at a level that correlated with macrophage infiltration of the tissue and could inhibit insulin production by Langerhans islets *in vitro* [65]. Temelimab is being evaluated in a randomized placebo-controlled study for safety and pharmacodynamic response in T1D patients [66]. Among patients with new-onset disease, both HERV-H pol and HERV-W pol, but not HERV-K pol, transcript levels were found augmented in blood leukocytes [67]. The HERV-K env protein was also expressed as cognate antibodies were detected in patients, with the highest level seen at disease onset [68]. Of note, Coxsackievirus B4 (CVB4), an enterovirus extensively studied for a suspected contribution to T1D pathogenesis, can activate HERV-W/MSRV env transcription in primary cultures of monocytes, macrophages, and pancreatic cells [69], suggesting that if HERV neo-expression can contribute to break tolerance to islet antigens, infection with exogenous virus may play a role in HERV induction.

Other Inflammatory/Autoimmune Disorders

There exist additional inflammatory/autoimmune disorders for which some association between HERVs and pathological features are considered. At least four such associations are noticeable.

(I) Autoimmune hepatitis (AH) is a poorly understood multifactorial liver disease characterized by abnormal immune responses toward liver antigens expressed by hepatocytes and cholangiocytes with persistent inflammation of the tissue. AH patients harbor hypergammaglobulinemia, circulating autoantibodies and lympho-plasmocytic infiltration. In this context, it was observed that ER stress initiated by HERV1 env expression could stimulate both an unfolded protein response [70] and an abnormally elevated level of reverse transcriptase activity [71].

(II) Psoriasis is a chronic inflammatory disorder that involves an inappropriate activation of innate immune cells and autoreactive T cells leading primarily to skin inflammation and keratinocyte hyperproliferation. IL-17 secreted by CD4 T cells and IL-23 plus TNFα secreted by dendritic cells are important players in the pathogenesis. Both genetic (eg, HLA-C*06:02 class I molecules) and environmental triggers appear involved. It was noticed that members of the HERV-K and -W families are overexpressed in psoriasitic skin lesions [72,73] and interestingly, single nucleotide polymorphism (SNP) variants of the HERV-K deoxyuridine 5'-triphosphate nucleotidohydrolase (UTPase) enzyme were found to either associate with, or protect from, disease susceptibility [74].

(III) Sjogren's syndrome (SS) is a chronic autoimmune pathology that mainly affects the salivary and lacrimal glands causing severe dryness of the mouth and eyes. Both abnormally activated T and B cells participate in the process that causes the destruction of exocrine gland epithelial cells. Of note, a sizable portion of SS patients present an additional autoimmune disorder such as RA or SLE, raising the question of a possible role for cross reactivity to distinct tissue antigens by clonally distributed antigen receptors. Humoral responses toward both HERV3-1 envelope glycoprotein and HERV4.1 p30 gag protein were observed in SS patients [46,75].

(IV) Pemphigus constitutes a type of IgG-mediated autoimmune disorders that affect stratified epithelia spe-

cially in the skin where the loss of keratinocyte adhesion causes blisters and erosion. In Pemphigus vulgaris, IgG autoantibodies react to adhesion factors involved in desmosome formation. The activation of CD4 and CD8 T cells that react to self-antigens presented on dendritic cells are important in promoting the generation of autoantibodies with a particular role for Th2 helper T cells. Pemphigus vulgaris was found to associate with an augmented expression of HERV-W env [76] and elevated transcript level of HERV-K, HERV-W, and HERV-H [77].

CONCLUDING REMARKS

Despite observations that point to a putative role for HERV expression in the pathogenesis of immunological disorders, our knowledge of HERV-associated activation of the proinflammatory pathway and the way it relates to autoimmunity remain largely fragmentary and speculative. We basically know little about the ways neo-expressed HERV nucleic acids and proteins are susceptible to mechanistically contribute to the development of particular autoimmune diseases. Among major difficulties in studying the immunopathological consequences of HERV neo-expression are the fact that the modeling of HERV expression consequences in common animal models is complicated by the preexisting set of species-associated endogenous retroelements acquired during evolution and the fact that other (non-HERV) endogenous retroelements, such as LINEs and SINEs are susceptible to also modulate immune responses. A fine molecular dissection of HERV expression, the mechanisms at play and an understanding of the associated functional consequences are needed before HERV-specific therapeutic approaches may be envisioned. Neutralizing the effects of deregulated HERV expression in autoimmunity could obviously involve the delivery of reverse transcriptase inhibitors. However, such inhibitors may also interfere with the controlled expression of some HERV factors that participate in cell homeostasis at steady state, including in relation with the immune system. In terms of HERV-specific treatments, therapeutic interventions may rely on HERV-protein specific immuno-therapies (both monoclonal antibodies and chimeric antigen receptor (CAR) T cells), possibly in combination with anti-inflammatory biotherapies. Finally, recombinants viruses engineered for HERV factor expression could be considered in order to promote anti-HERV humoral responses provided that such viruses do note trigger unwanted HERV neo-expression by themselves. Overall, these approaches will require a clear demonstration of a central role for the expression of the considered HERV(s) in the autoimmune disorder of interest.

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