Vol 3:7-15

JEMI-PEARLS

Human Endogenous Retroviruses as Contributors of Exosome-mediated Autoimmunity in Systemic Lupus Erythematosus

Haya AbuZuluf[a]

[a]Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada

SUMMARY At least 8% of the human genome was formed by integration of retroviral DNA sequences. These sequences are remnants of ancient infections that have accumulated mutations over millions of years. Although human endogenous retroviruses (HERVs) were previously thought to be inactive, they are now emerging as potential contributors of autoimmune diseases. Environmental and epigenetic factors have been shown to activate the expression of HERVs in pathological conditions such as Systemic Lupus Erythematosus (SLE). SLE is a poorly understood non-organ specific autoimmune disease lacking diagnostic criteria and curative treatments. It has been suggested that an unfortunate interplay of genetic susceptibility and environmental factors play an important role in generating an abnormal autoimmune response in SLE patients. HERVs have been proposed to be the bridge linking environmental factors to the pathogenesis of SLE. However, no clear mechanisms of causation have been identified in this association. This review outlines the key HERVs implicated in SLE, the factors that influence their activation and the proposed mechanisms utilized by HERVs in the etiopathogenesis of SLE. In addition, I investigate the potential of exosomes in playing a role in HERV-mediated stimulation of the immune system that in turn may contribute to activation and progression of SLE. The characterization of exosomal cargo will allow the identification of HERV products or sequences that may be transmitting intercellular signals involved in the immune dysregulation of SLE. Elucidating this association between HERVs and SLE may facilitate the development of novel diagnostic and therapeutic tools to combat this debilitating multi-system disease.

Accepted: 23 July 2018
Published: 01 August 2018
Citation: AbuZuluf H. 2018. Human Endogenous Retroviruses as Contributors of Exosome-mediated Autoimmunity in Systemic Lupus Erythematosus. JEMI PEARLS 3:7-15
Editor: François Jean, University of British Columbia
Copyright: © 2018 Journal of Experimental Microbiology and Immunology. All Rights Reserved.
Address correspondence to Haya AbuZuluf hayazuluf04@gmail.com

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune rheumatic disease that is highly heterogeneous in its manifestation [1]. It is characterized by periods of active disease, known as flares, and periods of remission during which there are few symptoms [2]. A broad spectrum of clinical presentations appear along with interpatient

variability. This includes dermatological, musculoskeletal, haematological, cardiopulmonary, renal and neuropsychiatric manifestations [2].

Prevalence of SLE is variable and ranges from 40 to 200 per 100,000 [3]. This depends on the ethnic and geographic differences in the population being studied, the definition of SLE applied and the methods of case identification [3, 4]. SLE is more common in those of African and Asian ancestry and is nine times more prevalent in females than males [4]. The usual onset of the disease is between 15-45 years old, although it can appear at any age [4].

Being a non-organ specific disease makes it highly unpredictable and poses challenges to physicians responsible for the diagnosis and management of the disease. It takes an average of 6 years to get a definite SLE diagnosis, from the time symptoms appear [5]. By that time, many will develop serious complications such as kidney disease, cardiovascular problems and chronic arthritis [4]. Lupus nephritis (LN) is a major cause of the morbidity and mortality of SLE, where up to 30% of patients progress to end-stage renal disease [6]. The majority (63%) of SLE patients report being incorrectly diagnosed [5]. Of those, more than half (55%) report seeing four or more different healthcare providers for their symptoms before being accurately diagnosed [5]. Diagnostic criteria have not been developed yet, although classification criteria made for research purposes have been adopted for aid in clinical diagnoses [7]. The 1997 American College of Rheumatology (ACR) criteria has been revised in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC), requiring patients to meet at least four out of 17 criteria to get a definite diagnosis [7, 8]. However, none of these classification criteria have 100% sensitivity and 100% specificity and may still fail to classify some patients [8]. Therefore, there is an urgent need for diagnostic tools to help in early detection and management of the disease.

Although the cause of SLE is still unknown, evidence suggests a complex interplay between genetic, epigenetic and environmental factors [9]. The disease is primarily driven by loss of immune tolerance and abnormal innate and adaptive responses [1]. One of the main candidates currently implicated in the etiopathogenesis of SLE are human endogenous retroviruses (HERVs) [10]. The observation of a long preclinical duration preceding the clinical onset of the disease, analogous to clinical symptoms of retrovirus infections, led to the proposal of endogenous retrovirus involvement in autoimmune diseases [10]. In light of relevant literature emerging in the field, this relationship is further examined in this article.

It has been suggested that certain factors activate the expression of HERV elements [9]. This activation can influence the function of critical immune responses, leading to immune dysregulation or dysfunction characteristic of SLE [9]. Therefore, understanding the role HERVs play in the pathogenesis of SLE will facilitate the move towards developing targeted therapies that prevent their activation. This article will describe the potential of HERVs as the bridge linking the multifaceted factors predicted to cause SLE.

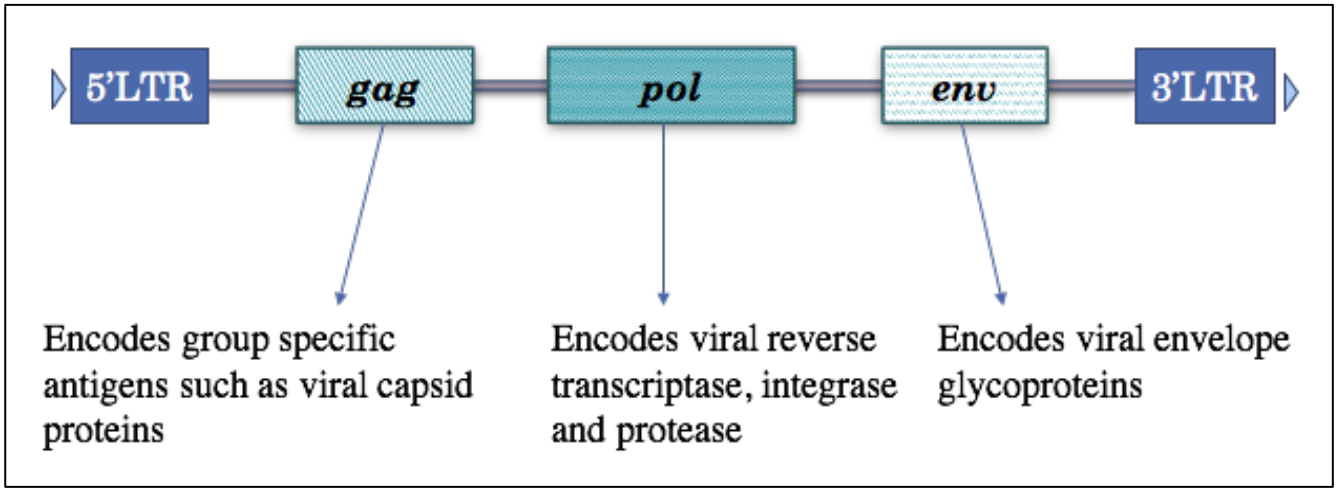

FIG. 1 Structure of intact HERV DNA. HERVs are similar to exogenous retroviruses in that they are composed of *gag*, *pol* and *env* genes, flanked by LTRs. *gag* stands for group specific antigens which encodes viral capsid proteins and nucleocapsids. *pol* encodes for the viral polymerase, composed of the reverse transcriptase, integrase and protease. *env* encodes for the viral envelope proteins.

RESEARCH QUESTIONS

SLE is a multifactorial disease that can be debilitating to affected individuals. There is no cure for SLE and current treatments are only aimed at easing symptoms [11]. In addition to SLE affecting the immune system, treatments will further reduce cellular and humoral responses due to their inhibition of T and B lymphocytes [11]. This weakened immune system can lead to secondary outcomes by predisposing patients to a range of infections and disorders that can be even more impairing than the disease itself. Since the aetiology of SLE is unknown, we have a limited ability to define the disease and design therapeutics that are able to target the disease directly.

HERVs have been emerging as candidates of autoimmune manifestations and not just "junk" DNA, as previously considered. Increasing evidence in the literature suggests that HERVs play a role in SLE, although there are no clear mechanisms of causation that have been identified. Therefore, I will present three research questions that will be address the link between HERVs and SLE. Firstly, the key HERV classes associated with the cause and/or subsequent development of SLE manifestations need to be identified, along with the factors that influence their expression or activation. Secondly, the proposed mechanisms utilized by HERVs in the etiopathogenesis of SLE need to be further explored. Finally, utilizing this information, this article aims to investigate the potential of endogenous retrovirus elements attributing to exosome-mediated autoimmunity in SLE patients.

PROJECT NARRATIVE

What are the key HERVs implicated in SLE and the factors influencing their activation?

Over the past few years, interest in HERVs as potential contributors to autoimmune diseases has increased [12-15]. The identification of the key HERVs implicated in SLE will allow us to study their structure and mechanisms of activation in order to subsequently elucidate their role in causing disease. HERVs are remnants of ancient infections which integrated into the germline 30 to 40 millions of years ago [16]. They are passed down through generations in a Mendelian fashion and constitute around 8% of human DNA [16]. Through phylogenetic studies, they have been classified into Class I, II or III and further categorized into families (e.g. HERV-K, HERV-R) [17]. Their structure is similar to exogenous retroviruses in that they are composed of *gag, pol* and *env* genes, which encode viral capsid proteins, reverse transcriptase and envelope proteins, respectively (Fig. 1) [17]. Additionally, they are flanked by long terminal repeats (LTRs), which contain the promoter and enhancer

HERV	Class	Region	Structure	Significance	References
HRES-1	Class I	Chromosome 1	LTR-*gag*-Δ*pol*	• Elevated antibodies to Gag- generated proteins in patients with active SLE • Integration into SLE susceptibility locus	23, 25, 26
HERV-R (ERV-3)	Class I	Chromosome 7	LTR-*gag*-*pol*-*env*-LTR	• Elevated antibodies to *env* products in SLE patients • Homology between SLE autoantigens and *env*	27, 28
HERV-E 4-1	Class I	Mapped to several chromosomes	LTR-*gag*-*pol*-*env*-LTR	• PBMCs from SLE patients generate mRNA *gag* transcripts • Autoantibodies to recombinant Gag products together with manifestations of SLE in an animal model	29, 30
HERV-K10/HERV-K18	Class II	Widely distributed, including chromosome 1	LTR-*gag*-*pol*-*env*-LTR	• Antibodies against HERV-K10 Gag- and Env- derived peptides found in SLE patients • Superantigens on HERV-K18	31, 37

TABLE 1 Summary of key HERVs implicated in the etiopathogenesis of SLE. This table outlines the class, region, structure and significance of HERV sequences that have been studied in relation to SLE. PBMCs refer to peripheral blood mononuclear cells. Δ refers to gene deletion.

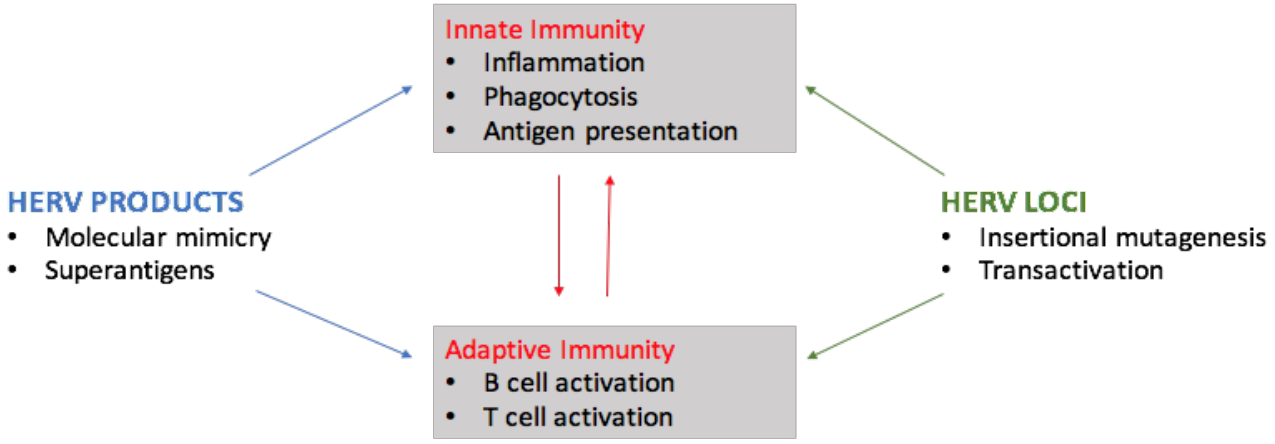

FIG. 2 A brief outline of proposed mechanisms utilized by HERV loci and gene products in the etiopathogenesis of SLE. HERV products might be involved in molecular mimicry, where homology between HERV amino acid sequences and SLE autoantigens can lead to cross reactive antibodies to epitopes on human tissues. Superantigens can activate a polyclonal expansion of autoreactive T cells. Alternatively, HERV sequences may be involved in insertional mutagenesis within or near genes necessary for proper regulation of the immune system. Transactivation of host genes may also have a role in overexpression of cytokines leading to abnormal systemic inflammation. The affected innate responses impact the adaptive immune system and vice versa.

regions important for viral transcription [17]. Although they are mostly inactive due to mutations and insertional events, increased expression and antibody reactivity to HERV products have been detected in patients with autoimmune diseases, including SLE, multiple sclerosis, rheumatoid arthritis and type 1 diabetes (T1D) [17-19].

Table 1 summarizes the class, region, structure and significance of the key HERVs implicated in SLE. Among those, HTLV-1-related endogenous sequence (HRES-1) is the most studied in SLE [18-21]. HRES-1 has been mapped to chromosome 1 which has a number of susceptibility genes that predispose to SLE [22, 23]. Its LTR region has been found to contain particular alleles correlated to clinical manifestations of SLE. [24]. Studies have also shown SLE patients with clinically active disease producing high titer antibodies to HRES-1 Gag generated proteins [25, 26]. HERV-R is located on chromosome 7 and encodes a truncated Env polypeptide [27]. A key study highlighted a potential role of HERV-R in newborns with congenital heart block (CHB), an example of neonatal lupus syndrome [28]. The mothers of these babies were found to have elevated levels of antibodies to the HERV-R Env products [28]. HERV-E clone 4-1 is another key sequence found to generate mRNA *gag* transcripts in SLE patients [29]. Autoantibodies have been detected in SLE patients to recombinant HERV-E Gag proteins [30]. Moreover, the highly homologous HERV-K10 and HERV-K18 have been demonstrated to trigger antibody production through their *gag* matrix-derived peptide in renal lupus patients [31]. This association between different HERV elements and phenotypic manifestations of SLE should be further investigated.

These key HERVs have been shown to be influenced by estrogen, DNA hypomethylation and ultraviolet light (UVB) exposure [32, 33]. The 5' LTR of HERV-K10 contains a hormone responsive element shown to enhance transcription levels when stimulated with estrogen, hence the bias of SLE towards females [34]. Certain drugs such as procainamide have also been shown to enhance HERV expression due to inhibition of DNA methylation [32]. UVB irradiation in epidermal keratinocytes also causes transcriptional activation of HERVs through poorly understood mechanisms [35]. This however could be a possible explanation of lupus flares associated with sunlight exposure [35].

Viral infections could also play a synergistic relationship (e.g. notion of 'helper' viruses). Epstein Barr virus (EBV) has been highlighted as a potential agent that plays a co-operative role in the upregulation of HERV-K10 activity in SLE [36]. In addition to HERV activation, insertional and sequence polymorphisms within the genome may cause disease in some individuals but not others, as mentioned with HRES-1 polymorphic genotypes [24]. All of these factors may be a single cause or together play a role in modulating the involvement of HERVs in SLE pathogenesis.

What are the proposed mechanisms utilized by HERVs in the etiopathogenesis of SLE?

As mentioned previously, immune dysregulation and lack of immune tolerance are evident in SLE. Several mechanisms have been proposed as possible explanations by which retroviral endogenous elements can participate SLE disease progression (Fig. 2) [37]. The potential of HERVs to initiate and substantiate an autoimmune response can be through the effects of both its genes and gene products [37].

HERVs retain their ability to transposition and are subsequently found to integrate within or near host genes necessary for proper functioning of the immune response, such as *fas*, MHC and complement genes [37, 38]. An example of endogenous retroviral integration is evident in MRL/1pr mouse model, where HRES-1 integrates into the murine *fas* apoptosis-promoting gene [38]. This results in failure of apoptosis in autoreactive lymphocytes through decreased expression of Fas, leading to a severe systemic autoimmune disease in these mice similar to human SLE [38]. HERVs may also encode elements like Tat in HIV-1 or Tax in HTLV-1 which enable transactivation of cellular genes [37, 39]. In HIV-1-infected cells, Tat has been shown to activate the expression of tumor necrosis factor (TNF), involved in systemic inflammation [37, 39]. Therefore, it is possible that HERV encoded transactivating elements play a similar role to those encoded by HIV-1 or HTLV-1.

Alternatively, HERV gene products can sustain the disease by acting as superantigens or as cross-reactive antigens through molecular mimicry [37]. Sutkowski *et al.* showed that EBV, acting as an exogenous environmental factor, activates a superantigen on HERV-K18 [40]. Superantigens bind to conserved regions of MHC class II outside of the peptide-binding groove leading to expansion of T cell subsets and excessive cytokine production harmful to the host [40]. In addition, HERVs encode products that mimic common nuclear protein sequences such as sn-RNP [41]. This stimulates the production of antiretroviral antibodies that are cross-reactive with common nuclear antigens [41]. Perl *et al*. illustrated a correlation between the presence of antibodies to HRES-1 (found in 52% of SLE patients) and anti-RNP antibodies that may serve as a priming mechanism in the ongoing autoimmune response to self-antigens [42].

Studies that support the association between HERVs and SLE still remain limited. However, as the key HERVs implicated in autoimmunity emerge, further experimental evidence is needed to support the above proposed mechanisms. For the final question, I bridge these proposed mechanisms by hypothesizing a model by which HERVs hijack the exosome secretion pathway for induction of SLE pathogenesis.

Can HERV elements be attributed to exosome-mediated autoimmunity in SLE patients?

Exosomes are secreted, nano-sized membrane vesicles, 50-100 nm in diameter that contain DNA, RNA, proteins, lipids, and metabolites of producing cells [43]. They are released under both physiological and pathological conditions into the extracellular space, and in recent years, have been increasingly studied in association to several diseases [43]. Recently, Lee *et al.* found serum exosome levels to be significantly higher in SLE patients than healthy controls (HCs) and their levels correlate with disease activity [44]. SLE-isolated exosomes were found to induce a higher production of IFN-α, TNF-α, IL-1β and IL-6 compared to HCs-isolated exosomes [44]. This evidence suggests that circulating exosomes are immunologically active and contain potent immunomodulatory material associated with SLE pathogenesis. Therefore, exosomes may also be circulating HERV elements and propagating their pathogenic potential through direct or indirect mechanisms (Fig. 3). This model could lead to exciting research advances in understanding SLE pathogenesis and developing diagnostic and therapeutic tools.

HERVs could utilize the exosomal pathway to directly spread signals which may dis-regulate or disrupt genes critical in normal functioning of the immune system, for example insertional mutagenesis or transactivation as described previously. Recent evidence revealed a newly discovered ability of a retrovirus-like Gag protein, known as Arc1, in auto-assembling and forming a virus-like capsid [45, 46]. This capsid structure was found to bind copia mRNA, a common *Drosophila* retrotransposon, and traffic across synapses in the nervous system via exosomes [45, 46]. This process is thought to mediate intercellular RNA transfer and play a role in synaptic plasticity [45, 46]. Arc's evolutionary history is not fully understood, however recent studies have suggested that Arc emerged from a vertebrate

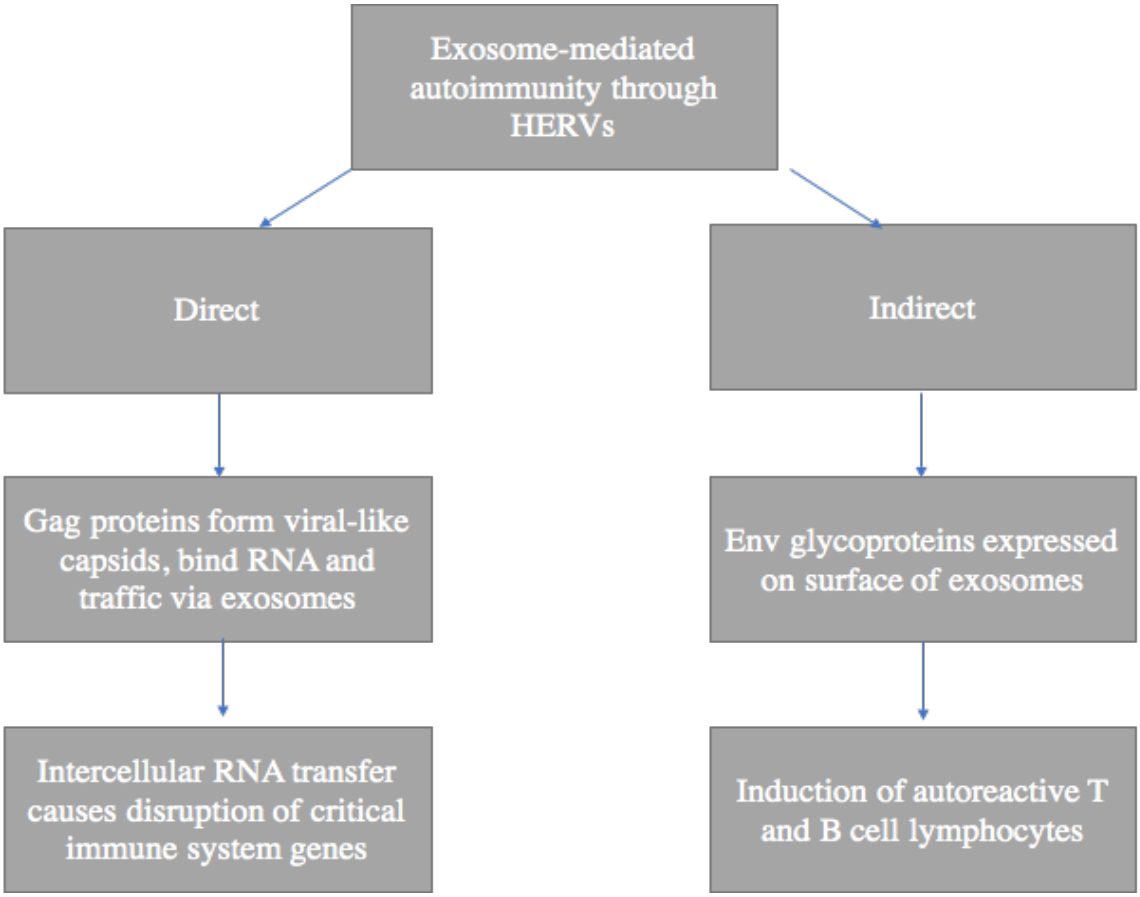

FIG 3 Proposed model of HERV exosome-induced autoimmunity in SLE patients. This flowchart outlines the proposed role of exosomes in acting as immunostimulatory particles by propagating pathogenic potential of HERVs through direct or indirect mechanisms.

lineage of Ty3/gypsy retrotransposons, which are also ancestors to retroviruses [46-48]. Therefore, the presence of other Arc-like proteins encoded by HERVs is possible. Investigating the identity of the RNAs that bind into these capsids and undergo secondary envelopment by exosomal membranes will be essential to unravel the role of HERVs in SLE.

Alternatively, exosomes can expose HERV elements such as Env glycoproteins on their surface, mediating indirect autoimmune induction. Exosomes express both self-antigens and peptide-MHC complexes and therefore, they could represent a source of HERV antigens that might activate autoreactive T cells in the context of MHC [49]. A recent study found endogenous retrovirus (ERV) proteins enriched in exosomes secreted in T1D mouse models [50]. These ERV antigens were found to be targets of autoreactive T and B lymphocytes and attributed to the autoimmune induction [50].

In summary, exosomes can potentially serve as “nano-shuttles” that spread HERV information, leading to the systemic manifestation of SLE. Their cargo can range from viral RNAs, proteins and surface antigens that potentially induce autoimmunity through direct and/or indirect mechanisms. This might explain the role of HERVs in the initiation and perpetuation of the autoimmune response in SLE.

SUMMARY AND CONCLUSION

SLE is the prototype multisystem autoimmune disease that presents as the great mimic to many other diseases due to its wide spectrum of clinical manifestations [1, 2]. Although relatively common throughout history, very limited advancements have been made in facilitating the diagnosis and development of therapeutics that directly target SLE [6-8]. HERVs represent a key molecular link between the environmental and genetic factors that govern SLE etiopathogenesis [18, 33]. Understanding this complex interplay and mechanisms

by which HERVs are associated with SLE can provide insight into the potential contribution of endogenous viruses in the development of other multifactorial autoimmune diseases.

The purpose of this review was to outline the associations of HERVs in SLE and to analyse possible means by which these associations could lead to the onset or exacerbation of this non-organ specific disease. This article also presents a model by which HERVs exploit exosomal pathways to induce abnormal immune responses characteristic of SLE. Studies that examine the role of HERVs in SLE are very limited due to the challenges that arise with this disease. However, as HERVs emerge in having a role in pathological conditions, further experimental evidence is needed to support the research questions presented in this article. Once the causative mechanisms of HERV involvement in SLE are unravelled, new frontiers open up for biomarker detection to track and monitor disease progression and therapeutic strategies for treatment of the disease. Additionally, it will enable a more refined definition of SLE and the development of diagnostic criteria with enhanced sensitivity and specificity.

Future studies should focus on experimentally proving the associations of the key HERVs presented in this article and other environmental and epigenetic factors that might influence their activation. The pathological mechanisms explored in this article should be further investigated and put into context with the proposed exosome-mediated autoimmunity model. This can be done through a multicentre study cohort consisting of HCs, SLE lab-confirmed cases (definite, probable and possible), those with currently active versus low level activity SLE, and other types of lupus (e.g. cutaneous, drug-induced and neonatal lupus). Isolation and purification of exosomes from these individuals' biofluids will allow characterization of the cargo in healthy and diseased samples. Deep sequencing and tandem mass spectrometry should subsequently be performed to establish transcriptomic and proteomic profiles for each sample, which will allow thorough comparison of exosomal content.

ACKNOWLEDGEMENTS

I would like to thank Dr. Jean for his constant assistance and support during the development of my project. His guidance was extremely helpful when it came to writing this paper.

REFERENCES

1. Shaikh MF, Jordan N, D'Cruz DP. 2017. Systemic lupus erythematosus. Clin Med 17:78-83.
2. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. 2011. Manifestations of Systemic Lupus Erythematosus. Mædica 6:330-336.
3. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. 2014. The incidence and prevalence of systemic lupus erythematosus, 2002-2004: The Georgia Lupus Registry. Arthritis Rheumatol 66:357-68.
4. Stojan G, Petri M. 2018. Epidemiology of systemic lupus erythematosus: an update. Curr Opin Rheumatol 30:144-150.
5. Al Sawah S, Daly R.P, Foster S, Naegeli A, Benjamin K, Doll H, Bond G, Moshkovich, O, Alarcon G. 2015. Understanding Delay in Diagnosis, Access to Care and Satisfaction with Care in Lupus: Findings from a Cross-Sectional Online Survey in the United States. Annals of the Rheumatic Diseases 74:812.
6. Almaani S, Meara A, Rovin BH. 2017. Update on Lupus Nephritis. Clin J Am Soc Nephrol 12:825-835.
7. Larosa M, Iaccarino L, Gatto M, Punzi L, Doria A. 2016. Advances in the diagnosis and classification of systemic lupus erythematosus. Expert Rev Clin Immunol 12:1309-1320.
8. Hanly JG. 2004. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus 13:861-4.
9. Kamen DL. 2014 Environmental influences on systemic lupus erythematosus expression. Rheum Dis Clin North Am 40:401-12.
10. Fierabracci A. 2009. Unravelling the role of infectious agents in the pathogenesis of human autoimmunity: the hypothesis of the retroviral involvement revisited. Curr Mol Med 9:1024-33.
11. Amissah-Arthur MB, Gordon C. 2010. Contemporary treatment of systemic lupus erythematosus: an update for clinicians. Ther Adv Chronic Dis 1:163-75.
12. Ejtehadi HD, Freimanis GL, Ali HA, Bowman S, Alavi A, Axford J, Callaghan R, Nelson PN. 2006. The potential role of human endogenous retrovirus K10 in the pathogenesis of rheumatoid arthritis: a preliminary study. Ann Rheum Dis 65:612-6.
13. Hurst TP, Magiorkinis G. 2015. Activation of the innate immune response by endogenous retroviruses. J Gen Virol 96:1207-18.
14. Manghera M, Douville RN. 2013. Endogenous retrovirus-K promoter: a landing strip for inflammatory transcription factors? Retrovirology 10:16.

15. Nexø BA, Villesen P, Nissen KK, Lindegaard HM, Rossing P, Petersen T, Tarnow L, Hansen B, Lorenzen T, Hørslev-Petersen K, Jensen SB, Bahrami S, Lajer M, Schmidt KL, Parving HH, Junker P, Laska MJ. 2016. Are human endogenous retroviruses triggers of autoimmune diseases? Unveiling associations of three diseases and viral loci. Immunol Res 64:55-63.
16. Gifford R, Tristem M. 2003. The evolution, distribution and diversity of endogenous retroviruses. Virus Genes 26:291-315.
17. Vargiu L, Rodriguez-Tomé P, Sperber GO, Cadeddu M, Grandi N, Blikstad V, Tramontano E, Blomberg J. 2016. Classification and characterization of human endogenous retroviruses; mosaic forms are common. Retrovirology 13:7.
18. Tugnet N, Rylance P, Roden D, Trela M, Nelson P. 2013. Human Endogenous Retroviruses (HERVs) and Autoimmune Rheumatic Disease: Is There a Link? Open Rheumatol J 7:13-21.
19. Blomberg J, Ushameckis D, Jern P. 2000. Evolutionary Aspects of Human Endogenous Retroviral Sequences (HERVs) and Disease. Madame Curie Bioscience Database.[Internet].
20. Gergely P Jr, Pullmann R, Stancato C, Otvos L Jr, Koncz A, Blazsek A, Poor G, Brown KE, Phillips PE, Perl A. 2005. Increased prevalence of transfusion-transmitted virus and cross-reactivity with immunodominant epitopes of the HRES-1/p28 endogenous retroviral autoantigen in patients with systemic lupus erythematosus. Clin Immunol 116:124-34.
21. Perl A, Fernandez D, Telarico T, Phillips PE. 2010. Endogenous retroviral pathogenesis in lupus. Curr Opin Rheumatol 22:483-92.
22. Tsao BP. 2000. Lupus susceptibility genes on human chromosome 1. Int Rev Immunol 19:319-34.
23. Tsao BP, Cantor RM, Kalunian KC, Chen CJ, Badsha H, Singh R, Wallace DJ, Kitridou RC, Chen SL, Shen N, Song YW, Isenberg DA, Yu CL, Hahn BH, Rotter JI. 1997. Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. J Clin Invest 99:725-31.
24. Magistrelli C, Samoilova E, Agarwal RK, Banki K, Ferrante P, Vladutiu A, Phillips PE, Perl A. 1999. Polymorphic genotypes of the HRES-1 human endogenous retrovirus locus correlate with systemic lupus erythematosus and autoreactivity. Immunogenetics 49:829-34.
25. Brookes SM, Pandolfino YA, Mitchell TJ, Venables PJ, Shattles WG, Clark DA, Entwistle A, Maini RN. 1992. The immune response to and expression of cross-reactive retroviral gag sequences in autoimmune disease. Br J Rheumatol 31:735-42.
26. Perl A, Colombo E, Dai H, Agarwal R, Mark KA, Banki K, Poiesz BJ, Phillips PE, Hoch SO, Reveille JD. 1995. Antibody reactivity to the HRES-1 endogenous retroviral element identifies a subset of patients with systemic lupus erythematosus and overlap syndromes. Correlation with antinuclear antibodies and HLA class II alleles. Arthritis Rheum 38:1660-71.
27. Li JM, Fan WS, Horsfall AC, Anderson AC, Rigby S, Larsson E, Venables PJ. 1996. The expression of human endogenous retrovirus-3 in fetal cardiac tissue and antibodies in congenital heart block. Clin Exp Immunol 104:388-93.
28. Blank M, Shoenfeld Y, Perl A. 2009. Cross-talk of the environment with the host genome and the immune system through endogenous retroviruses in systemic lupus erythematosus. Lupus 18:1136-43.
29. Ogasawara H, Hishikawa T, Sekigawa I, Hashimoto H, Yamamoto N, Maruyama N. 2001. Sequence analysis of human endogenous retrovirus clone 4-1 in systemic lupus erythematosus. Autoimmunity 33:15-21.
30. Hishikawa T, Ogasawara H, Kaneko H. 1997. Detection of antibodies to a recombinant gag protein derived from human endogenous retrovirus clone 4-1 in autoimmune diseases. Viral Immunol 10:137-147.
31. Nelson NP, SHaw M, Roden D, Freimanis GL, Nevill AM, Rylance P. 2006. Human endogenous retrovirus HERV-K10 implicated in rheumatoid arthritis and systemic lupus erythematosus: potential pathological triggers? Biomed papers 150:29S-30S.
32. Okada M, Ogasawara H, Kaneko H, et al. 2002. Role of DNA methylation in transcription of human endogenous retrovirus in the pathogenesis of systemic lupus erythematosus. J Rheumatol 29:1678–1682.
33. Nelson P, Rylance P, Roden D, Trela M, Tugnet N. 2014. Viruses as potential pathogenic agents in systemic lupus erythematosus. Lupus 23:596-605.
34. Ejtehadi HD, Martin JH, Jung J. 2005. A novel multiplex RT-PCR system detects human endogenous retrovirus-K in breast cancer. Arch Virol 150:177–184.
35. Balada E, Vilardell-Tarre's M, Ordi-Ros J. 2010. Implication of human endogenous retroviruses in the development of autoimmune diseases. Int Rev Immunol 29: 351–370.
36. Freimanis G, Hooley P, Ejtehadi HD. 2010. A role for human endogenous retrovirus-K (HML-2) in rheumatoid arthritis: investigating mechanisms of pathogenesis. Clin Exp Immunol 160: 340–347.
37. Adelman MK, Marchalonis JJ. 2002. Endogenous retroviruses in systemic lupus erythematosus: candidate lupus viruses. Clin Immunol 102:107-16.
38. Wu J, Zhou T, He J, Mountz JD. 1993. Autoimmune disease in mice due to integration of an endogenous retrovirus in an apoptosis gene. J. Exp. Med 178:461–468.
39. Lower R, Tonjes RR, Korbmacher C, Kurth R, Lower J. 1995. Identification of a Rev-related protein by analysis of spliced transcripts of the human endogenous retroviruses HTDV/ HERV-K. J. Virol 69:141-149.
40. Huber BT, Hsu PN, Sutkowski N. 1996. Virus-encoded superantigens. Microbiol Rev 60:473-82.

41. Trela M, Nelson PN, Rylance PB. 2016. The role of molecular mimicry and other factors in the association of Human Endogenous Retroviruses and autoimmunity. APMIS 124:88-104.
42. Perl A, Isaacs CM, Eddy RL, Byers MG, Sait SN, Shows TB. 1991. The human T-cell leukemia virus-related endogenous sequence (HRES-1) is located on chromosome 1 at q42. Genomics 11:1172–1173.
43. Tan L, Wu H, Liu Y, Zhao M, Li D, Lu Q. 2016. Recent advances of exosomes in immune modulation and autoimmune diseases. Autoimmunity 49:357-365.
44. Lee JY, Park JK, Lee EY, Lee EB, Song YW. 2016. Circulating exosomes from patients with systemic lupus erythematosus induce a proinflammatory immune response. Arthritis Res Ther 18:264.
45. Ashley J, Cordy B, Lucia D, Fradkin L, Budnik V, Thomson T. 2018. Retrovirus-like Gag Protein Arc1 binds RNA and traffics across Synaptic boutons. Cell 172:262-274.
46. Pastuzyn, ED, Day CE, Kearns RB, Kyrke-Smith M, Taibi AV, Mccormick J. 2018. The Neuronal gene Arc encodes a repurposed retrotransposon Gag protein that mediates Intracellular RNA transfer. Cell 172:275-288.
47. Shepherd JD. 2017. Arc - An endogenous neuronal retrovirus? Semin Cell Dev Biol 30471-8.
48. Llorens C1, Fares MA, Moya A. 2008. Relationships of gag-pol diversity between Ty3/Gypsy and Retroviridae LTR retroelements and the three kings hypothesis. BMC Evol Biol 8:276.
49. Buzas EI, Gyorgy B, Nagy G, Falus A, Gay S. 2014. Emerging role of extracellular vesicles in inflammatory diseases. Nature Rev Rheumatol 10:356-64.
50. Dai Y, Bashratyan R, Regn D, Binley J, Marquardt K. 2015. Identification of endogenous murine leukemia retrovirus antigens attributing to exosome-induced autoimmunity in NOD mice (BA6P.122). J Immunol 194.

ACRONYMS

Systemic Lupus Erythematosus (SLE), Human endogenous retrovirus (HERVs), Lupus nephritis (LN), American College of Rheumatology (ACR), Systemic lupus international collaborating clinics (SLICC), long terminal repeat (LTR), Human T-cell lymphotrophic virus- related endogenous sequence type 1 (HRES-1), endogenous retrovirus type R (HERV-R), endogenous retrovirus type E (HERV-E), endogenous retrovirus type K (HERV-K), Type 1 diabetes (T1D), Congenital heart block (CHB), Ultraviolet radiation (UBV), Epstein Barr virus (EBV), endogenous retrovirus (ERV), Human immunodeficiency virus type 1 (HIV-1), Human T-cell lymphotrophic virus (HTLV-1), Tumor necrosis factor (TNF), small nuclear ribonucleoprotein (snRNP), healthy controls (HCs), interferon alpha (IFN-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), Major histocompatibility complex (MHC).