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Manuscript Title: HERV and Epstein-Barr Virus: another piece to Multiple Sclerosis puzzle

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Keywords: "Multiple Sclerosis", "HERV", "MSRV", "Epstein Barr Virus"

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HERV and Epstein-Barr Virus: another piece to Multiple Sclerosis puzzle

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Keywords: "Multiple Sclerosis", "HERV", "MSRV", "Epstein Barr Virus"

Abstract: Multiple Sclerosis (MS) has a well established link with Epstein-Barr virus (EBV) and a growing association with human endogenous retroviruses (HERVs). In this review, we described how these two pieces may interact in MS pathogenesis.

Introduction

Multiple Sclerosis (MS) is a fascinating disease that leads to Central Nervous System (CNS) inflammatory lesions and demyelination. It is a globally increasing condition, considered the most non-traumatic disable disease in young adult population (Morandi et al. 2017; Dobson 2018). MS has several unique factors, such as its classical association with higher latitudes, intriguing pathology, women preponderance and a widely variety of clinical presentations

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[Lassman 2019; Kantarci 2019; Noubarksh 2019]. The disease has three phenotypes: Remittent Relapsing (RRMS), Primary Progressive (PPMS) and Secondary Progressive (SPMS) [Dobson 2018; Arneth 2018].

The most acceptable hypothesis for MS aetiology is an autoimmune processes triggered by environmental (vitamin D, UVB light exposure, smoking [Dobson 2018] and genetic factors [de la Hera et al. 2014]. HLA-DRB1*15:01 constitutes the main genetic risk for the disease, although more than 150 single nucleotide polymorphisms (SNP) have been associated [Dobson 2018]. Viruses also play an important role in MS pathogenesis, both endogenous (HERV) and exogenous (Epstein-Barr, Herpes simplex, Human Hervesvirus 6A) ones [de la Hera et al. 2014; Fierz 2017].

This strong association with pathogens made Kurtzke et al suggest MS as a infectious driven disease especially after studied a strange epidemiological pattern in the Faroe Islands suggesting 4 MS epidemics [Kurtzke 1993; Kurtzke 1995]. This fact was contested by Joensen et al [Joensen 2010].

The human immunodeficiency virus (HIV) pandemic with MS like syndromes described [Delgado 2014] and the subsequent discovery of human T-lymphotropic virus (HTLV) and its chronic myelopathy syndrome put retroviruses in evidence as plausible answers for the MS puzzle [Gessein 2012].

Although the studies failed to prove any evidence of this viruses in MS patients [Christensen et al. 1997; Ramussen 1992; Stefanou et al. 2019] the research in this field started to bring interesting questions, such as antibodies against reverse transcriptase in MS patients

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with no evidence of retroviruses infection [Perron 1991], or an uncharacterized retrovirus like particles being produce in a B-lymphoblastoid cell line infected with Epstein-Barr virus (EBV) [Haahr 1992].

In the time of these articles the concept of human endogenous retroviruses was being settled [Urnovitz 1996] and that was probably the findings these authors were having back then.

HERV

Human Endogenous Retrovirus (HERVs) were integrated in human genome after ancestrals infections, about 30 to 70 million years ago [Morandi et al. 2017], and now constitute about 8% of the human genome [Grandi 2018]. Viral machinery allows HERVs to convert its RNA into double stranded DNA and to integrate into host genome [Douville 2014].

The basic structure of HERV is similar to exogenous retroviruses -- four main genes: gag, pro, pol and env (5-gag-pro-pol-env-3) [Douville 2014] and two LTR (Long Terminal Repeat) [Morandi et al. 2017]. Gag portion encodes matrix, capsid and nucleocapsid; Pro encodes Viral Protease; Pol encodes Reverse Transcriptase and Integrase and Env encodes envelope (surface and transmembrane subunits) [Grandi 2018; Douville 2014] – figure 1.

HERV proteins are usually inactive, but they seem to play an important role in several diseases (multiple sclerosis, neoplasm, Systemic Lupus Erythematosus [Manghera 2014]) and even non-pathological events, which is the case of HERV-W syncytin-1 (7q21.2 [Grandi 2018]), that contribute to placental formation due its fusogenic potential [Garcia-Montojo 2018].

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Interestly, *Garcia-Montojo* et al. demonstrated that Multiple Sclerosis patients have higher levels of syncytin-1 than control group, besides presenting activated phenotype in syncytin-1 expressing cells -- monocytes, lymphocytes (both T and) and Natural Killer -- and elevated levels of this protein in monocytes during MS relapses [Garcia-Montojo et al. 2020].

HERVs are divided into families, of which HERV-W has a vaster literature [Kremer et al. 2019; Dolei 2009; Grandi 2017; Grandi 2018] of correlation with MS; although HERV-H, HERV-Fc1 and HERV-K are also described in the disease [Morandi et al. 2017].

HERV-W is believed to be the most involved in MS pathogenesis, and it probably happens because of its components, MSRV and ERVWE [Arneth 2018; Bahrami 2018]. *Mameli* et al. have described these two components, whose ORFs origin MSRVenv (HERV-W env) and syncytin-1, respectively [Mameli et al. 2009]. MSRV (MS-associated Retrovirus) may induce T cells responses and proinflammatory cytokines release [Arneth 2018; Dolei 2009; Mameli et al. 2009].

In 2002, *Dolei* et al. described a cohort of 113 individuals of Sardinian origin, 39 of them having MS diagnosis. Of the MS diagnosed patients, 50% had positive CSF for MSRV, increasing with disease duration [Dolei et al. 2002]; suggesting that MSRV may be related to disease stage and progression [Mameli et al. 2009].

HERV proteins may trigger both innate and adaptive immune responses [Grandi 2018]. After Toll Like Receptor 4 (TLR 4) recognition, HERV-W env can activate innate immune response, especially macrophages and microglia, resulting in major inflammation [Arneth 2018; Bahrami 2018; Grandi 2018; Gruchot 2019; Kremer et al. 2019]. HERVs mostly leads to

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M1 macrophages stimulation, the proinflammatory phenotype; more than the anti-inflammatory ones, M2 [Arneth 2018, Kremer et al. 2019]. M1 macrophages leads to reactive oxygen, nitrogen species and inflammatory cytokines release, and microglia cells also produce proinflammatory molecules [Kremer et al. 2019]. Dendritic cells are also activated [Dolei 2009; Greening 2019]. Interleukins IL-1 and IL-6 contribute to inflammation process [Grandi 2018], such as TNF [Arneth 2018].

Adaptive immune response, on the other hand, occur after Antigen-Presenting Cells (APCs), including B cells, present antigens to T lymphocytes, which suffers polyclonal activation [Dolei 2009], release high quantity of cytokines [Grandi 2018]; besides destroying other cells (cytotoxicity) [Grandi 2018; Guan 2019] and myelin proteins [Guan 2019].

Inflammation and T cells response against myelin protein lead to neuronal injury [Guan 2019; Manghera 2014; Kremer et al. 2019]. Meanwhile, as demonstrated by *Kremer* et al in rats, HERV-W env prejudice differentiation of Oligodendrocyte Progenitor Cells (OPC), activated to provide myelin repair, through nitrosative stress [Kremer et al 2013; Gottle et al. 2018]. The combination of these events results in neuroinflammation with not properly remyelination – figure 2.

HERV-H role is controversial, with some authors demonstrating higher levels of HERV-H env proteins in Peripheral Blood Mononuclear Cells (PMCB) in Multiple Sclerosis patients, compared with health and neurological controls [Brudek 2009]; and others authors demonstrating no difference [Morandi et al. 2017].

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Interestly, HERV-Fc1, located in X chromosome and closely related to HERV-H [Morris 2019], has also been associated with MS as demonstrated by *Nexo* et al. [Nexo et al. 2011] and *de la Hera* et al. [de la Hera et al. 2014]. *Laska* et al. described the presence of HERV-Fc1 gag RNA in all MS patients and healthy controls, and patients with active MS (median 1.6 x 10_7 copies/ml) had higher titers than inactive MS (median 5.1 x 10_6 copies/ml) and control group (median 4.2 x 10_6 copies/ml) [Laska et al. 2012]; and therefore it may be useful to define disease activity. Besides that, the location of this gene in X chromosome may contribute to the higher prevalence of MS in women [Nexo et al. 2011].

Epstein-Barr Virus and Multiple Sclerosis

Epstein-Barr virus (EBV) is an herpes virus capable of infecting and immortalizing B cells, leading to a latent infection at them [Hammerschmidt 2015]. It is known that EBV infection is an important environmental factor associated with Multiple Sclerosis [Dobson 2018]. A meta analysis provided evidence of EBV infection interaction with others MS risk factors in disease risk and its relevance as an isolated risk factor at all [Jacobs 2020] supporting and presenting evidence for the hypothesis presented by *Parkpoor* et al. that EBV infection is a prerequisite to disease development [Parkpoor et al. 2012]. Also, IgG antibodies against Epstein-Barr Virus-Encoded Nuclear Antigen-1 (EBNA-1) has been correlated with progression of the disease in Clinically Isolated Syndromes (CIS) presenting patients [Lunemann et al. 2010]. More recently, *Langer-Gould* et al. demonstrated association of EBV infection and increased risk of MS or CIS in white, black and Hispanic ethnic groups [Langer-Gould et al. 2017].

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When it comes to Epstein Barr Virus (EBV) infection, HERV-K18 has an important role [Manghera 2014; Us 2016]. Environmental factors, such as EBV virus, are important in HERV's transactivation [Groger 2018]. After EBV infection, memory B cells turn into reservoir for the latent virus [Guan 2019], which can transactivate HERV-K18 latter [Groger 2018]. HERV-K18 env proteins may act like Superantigens, which leads to T cell activation and major inflammatory response [Us 2016]. T lymphocytes, besides releasing cytokines, can also attack EBV infected cells [Guan 2019].

Scott et al. demonstrated EBV's ability to promote epigenetics alterations, as a form of establishing its latency and reactivation, and its role inducing methylation of tumor suppressing genes [Scott 2017]. In MS context, it was shown that EBV infection induced HERV-W elements (Syncytin-1 and MSRV) activation in astrocytes and blood cells through NF-kB pathway [Mameli et al. 2012]. Also, Hassani et al. contributed demonstrating that EBV is present in brain tissue and transcriptionally active in MS [Hassani 2018].

Conclusion:

In conclusion, EBV's epigenetic ability inducing HERV's activation in a variety of cells may play an important role in multiple sclerosis pathogenesis. This is an important piece in MS puzzle and should be more investigated, once there are new treatments for MS in development focusing in HERV mechanism, such as monoclonal antibodies targeting MSRV-Env protein [Curtin 2015] and antiretroviral therapy [Gold et al 2018; Morandi 2019].

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Conflicts of Interest

All authors declare that there is no conflicts of interests.

Authors contributions

All authors contributed equally for the article.

Availability of data and material

Not applicable.

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FIGURES

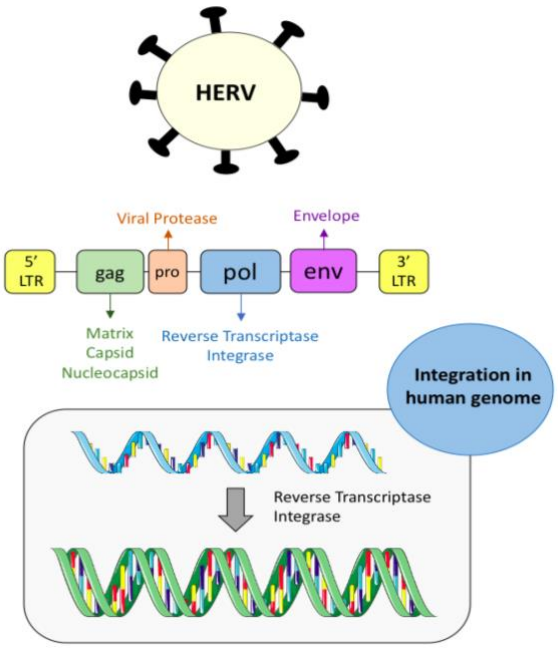

FIGURE 1: HERV's structure and integration in human genome. RNA and DNA illustrations obtained from Smart Servier website < *https://smart.servier.com* >

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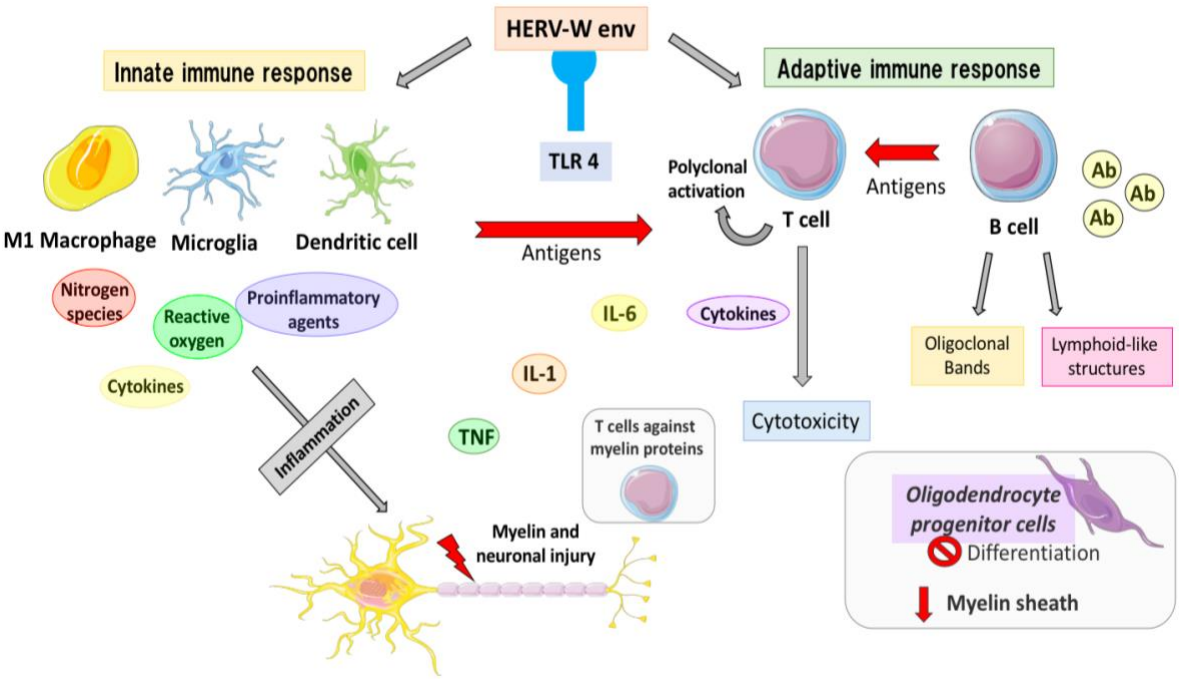

Figure 2: HERV-W env protein being recognized by Toll Like Receptor 4 (TLR 4) and triggering both innate and immune response. Neuronal injury occur due inflammation and cytotoxicity against myelin; while oligodendrocytes are unable to produce myelin sheath to replace. Cells illustrations obtained from Smart Servier website < *https://smart.servier.com* >