Journal of the Neurological Sciences 286 (2009) 65–72

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review

Endogenous retroviral genes, Herpesviruses and gender in Multiple Sclerosis

Hervé Perron [a,b,*], Corinne Bernard [a], Jean-Baptiste Bertrand [b], Alois B. Lang [a], Iuliana Popa [c], Kamel Sanhadji [d], Jacques Portoukalian [c]

[a] GeNeuro, 14 Chemin des Aulx, CH-1228 Plan-Les Ouates, Geneva, Switzerland
[b] GeNeuro-Innovation, Bioparc Lyon-Laënnec, 60 avenue Rockfeller, F-69008 Lyon, France
[c] Laboratory, EA 4169 University of Lyon1, Pavillon R, Hôpital Edouard Herriot, 69437 Lyon cedex, France
[d] Laboratory of Graft Immunology and Immunodeficiencies, Faculty of Medicine Laënnec, 69008 Lyon, France

ARTICLE INFO

Article history:
Received 30 January 2009
Received in revised form 2 April 2009
Accepted 14 April 2009
Available online 17 May 2009

Keywords:
Human endogenous retrovirus
HERV-W
MSRV
Multiple Sclerosis
Envelope protein
Syncytin
Herpesvirus
HSV1
EBV
HHV6
VZV
Chromosome X
TLR4
Immunopathology
Immunotherapy

ABSTRACT

Unexpected findings on endogenous retroviral elements expressed in cells from patients with Multiple Sclerosis appear to open a new avenue of research, after years of research dedicated to the understanding of their biological significance in human health and disease. Human endogenous retroviral family W (HERV-W) RNA present in circulating viral particles (Multiple Sclerosis associated RetroViral element, MSRV) has been associated with the evolution and prognosis of Multiple Sclerosis. HERV-W elements encode a powerful immunopathogenic envelope protein (ENV) that activates a pro-inflammatory and autoimmune cascade through interaction with Toll-Like Receptor 4 (TLR4) on antigen-presenting cells, and triggers superantigen-like dysregulation of T-lymphocytes. HERV-W/ENV antigen has further been shown to be an upstream inducer of immunopathogenicity like that in MS and has repeatedly been detected in association with MS lesions in post-mortem brain studies. ENV protein now represents a novel target in MS, in our ongoing development of a neutralising therapeutic antibody.

We here review the pieces of a puzzle, which now offer a consistent picture for Multiple Sclerosis aetiopathogenesis. Interestingly, at the gene–environment interface, this picture also includes gender-related specificities through the potential interplay with endogenous retrovirus type W copies present on the X chromosome.

Contents

1. Introduction

Retroviruses are characterised by their original capacity to integrate complete, recombined or partial copies of their genome into host cell DNA. Retroviral enzymes like reverse-transcriptase or integrase, as well as "sticky" nucleotide structures in flanking long terminal repeated sequences, are the major molecular vectors of these retroviral properties. Thus, unlike most viruses, retroviruses intimately interact with chromosomal DNA of infected individuals. It will thus be understood that, when infecting adult cells, this capacity to generate intra-chromosomal insertions will be limited to infected cells and to their cellular progeny as it is the case for classical exogenous retroviruses in

* Corresponding author. GeNeuro, 14 Chemin des Aulx, CH-1228 Plan-Les Ouates, Geneva, Switzerland.
E-mail address: hp@geneuro.com (H. Perron).

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doi:10.1016/j.jns.2009.04.034

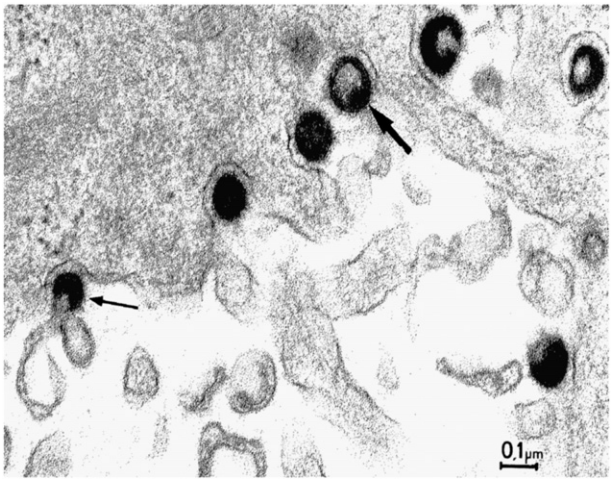

Fig. 1. MSRV element producing virions with RNA from HERV-W family visualized by electron microscopy (EM). Extracellular virion particles at the surface of leptomeningeal cells.

humans (e.g. Human Immunodeficiency Viruses or Human T-Leukaemia Viruses). It will also be understood that, when infecting germ-line cells (e.g. ovocytes), such retroviral insertions into chromosomes here provide a unique pathway to add transmissible sequences that will be present in all cells of individuals born from the fecundation of such genetically modified gamete. Moreover, as part of their inherited DNA, these retroviral sequences will further be transmitted to their progeny. During evolution of species, this phenomenon has frequently occurred and has generated an important category, though yet poorly studied and understood, of retroviral elements in-between viruses and transmissible genes but not subjected to the same selective genetic mechanisms as "normal genes". These elements that could also retain their property to retro-transpose into the host genome or to re-express viral particles in the extracellular space, are called "Endogenous Retroviruses".

In the following review, we shall explain how studies on retroviruses and Multiple Sclerosis (MS) have opened a new avenue of research in this quite unknown domain of "Human Endogenous Retroviruses". It will also argue how this domain now appears relevant in complex multifactorial diseases such as MS, notably through interactions with Herpesviruses and with their homologous endogenous multicopy family, with concrete therapeutic issues.

2. Endogenous retroviruses, genetics and disease

When the first descriptions of retrovirus-like particles with reverse-transcriptase (RT) activity in leptomeningeal LM7 and macrophage cell cultures from patients with Multiple Sclerosis (MS) were published [29,58,61] they were thought to be related to a new human T-lymphotropic virus (HTLV), able to explain homologies between HTLV-1 associated myelopathy and MS [36]. An example of such retroviral particles in MS cell cultures visualized by electron microscopy is presented in Fig. 1.

After successive biological characterisations of the MS-associated retroviral element (MSRV) [31,60,62,63,76], molecular characterisation of its genome was made possible [64,84]. This revealed quite a complex picture as the MSRV genome did correspond with those of retroviruses but, having endogenous counterparts in human DNA, belonged to the group of Human Endogenous Retroviruses (HERVs) [35]. Thus, it was not the expected new HTLV virus [36], but represented a previously unknown family of HERV elements, now named HERV-W [9,56]. The genome organisation of a prototypic MSRV sequence and the evolutionary tree of (H)ERV-W elements in primate genomes are schematically represented in Fig. 2.

Members of Endogenous Retrovirus families (ERVs) have been mostly studied in animals; for example mouse leukaemia viruses, mouse mammary tumour viruses and ovine pulmonary carcinoma viruses [5,6,10,19,89]. They are known to include few exogenous and/or horizontally transmissible strains. In fact endogenous retrovirus genomes apparently entered the germ line of most mammalian species millions of years ago through infectious events with virion-producing members, and have often spread within the species genomes through both Mendelian and non-Mendelian transmission [42,55,88]. Surprisingly, the recent sequencing of the human genome has revealed that over 40% of human DNA sequences belong to the category of repeated or (retro)transposable elements including endogenous retroviruses, themselves representing about 8% of the human genome [27,87]. The question of their biological significance in physiology and in diseases is now of considerable interest. It stands at the crossroads of genetics, virology and immunology; as they are both genes and viruses, and produce antigens that may or may not be tolerated by the immune system [23].

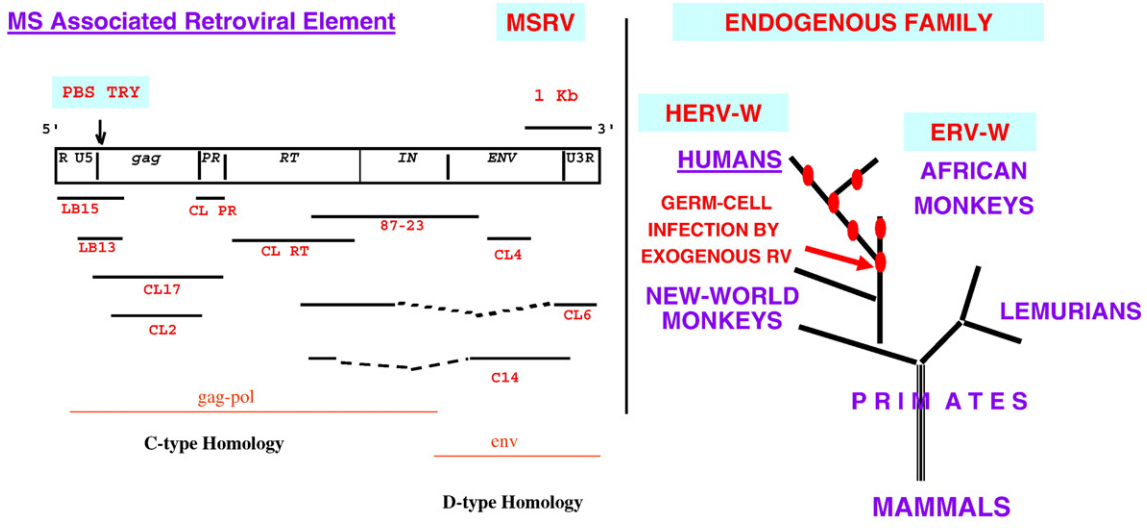

Fig. 2. Prototype RNA genomic organisation identified from extracellular MS virions (MSRV) and Phylogeny of corresponding HERV-W family. Left: The organisation of the RNA genome identified from purified MS retroviral particles was obtained from the first central sequence stretch identified in the "pol" gene [64] by 3′- and 5′ RT-PCR extension techniques, which yielded overlapping sequence amplifications as illustrated below the consensus genome structure [35]. Right: The schematic representation of the entry of Endogenous retroviral type W progeny in the germ line of superior primates, after initial infection by an exogenous member, illustrates corresponding genome studies [86].