5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 13

Nervous system disorders due to retroviruses (Level3)

The possible role of retroviruses in neurological disorders of unknown aetiology

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The possible role of retroviruses in neurological disorders of unknown etiology

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Outline

Virus etiology in MS

Retrovirology

HERV in MS

HERV in ALS

Conclusions

Viral etiology and MS

An infectious origin of MS was suggested for the first time by Pierre Marie in 1884

The topic is still relevant and unsettled

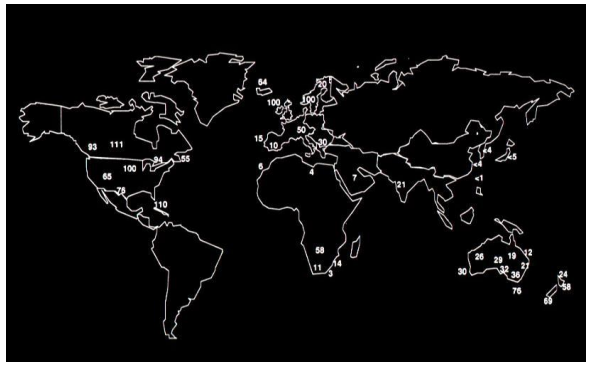
Viruses and MS: possible scenarios

1. Single initial viral infection initiates chronic immune-mediated inflammatory reaction
2. Recurrent viral infections due to same virus or different viruses that trigger a relapse
3. Reactivation of latent or persistent virus or viruses within the CNS

Evidence for Viral etiology of MS

1. Epidemiological Data
2. Laboratory Data in MS patients:
   a) Serological data
   b) Virus isolation
   c) Viral histochemistry & molecular studies
   d) Abnormalities of immune regulation
3. Animal models of Virus-Induced Demyelination

Epidemiological Data



Faroe Islands Data

Serology: Higher antiviral antibodies in MS than in controls

Serum

Measles
Parainfluenza 3
Influenza C
Varicella
Herpes simplex
Rubella
Epstein-Barr
HTLV-I (gag)
HTLV-II
HHV-6

CSF

Measles
Parainfluenzas 1-3
Influenza A, B
Varicella
Herpes simplex
Rubella
Epstein-Barr
Mumps
Respiratory syncytial

Coronaviruses
Adenoviruses
HTLV-I (gag)
Simian virus 5

Possible culprits: isolated viruses

- rabies virus,
- HSV,
- scrapie prion,
- parainfluenza virus 1,
- measles virus, simian virus 5,
- chimpanzee cytomegalovirus,
- coronavirus,
- EBV,
- tick-borne encephalitis virus,
- HTLV-1,
- VZV,
- HHV-6.

Proposed viral mechanisms:

- direct brain or peripheral infection
- activation of autoreactive T cells against nerve myelin
- bystander activation
- epitope spreading,
- molecular mimicry,
- virus–virus interactions.

Leptomeningeal cell line from MS with reverse transcriptase activity and viral particles.

H. Perron, C. Geny, A. Laurent, C. Mouriquand, J. Pellat, J. Perret, J.M. Seigneurin

In Vitro transmission and antigenicity of a retrovirus isolated from an MS patient

H. Perron , B. Gratacap, B. Lalande, O. Genoulaz, A. Laurent, C. Geny, M. Mallaret, P. Innocenti, E. Schuller, P. Stoebner, J.M. Seigneurin

Molecular identification of a noval retrovirus repeatedly isolated from patients with MS

H. Perron, J.A. Garson, F. Bedin, F. Beseme, G. Paranhos-Baccala, F. Komurian-Pradel, F. Mallet, P.W. Tuke, C. Voisset, J.L. Blond, B. Lalande, J.M. Seigneurin, B. Mandrand, and the Collaborative Research Group on Multiple Sclerosis.

MS and HTLV retrovirus

Hilary Koprowski, Elaine C. DeFreitas, Mary E. Harper, Magnhild Sandberg-Wollheim[3], William A. Sheremata[4], Marjorie Robert-Guroff, Carl W. Saxinger, Mark B. Feinberg, Fossie Wong-Staal, Robert C. Gallo

Amplification and molecular cloning of HTLV-1 sequences from DNA of MS patients

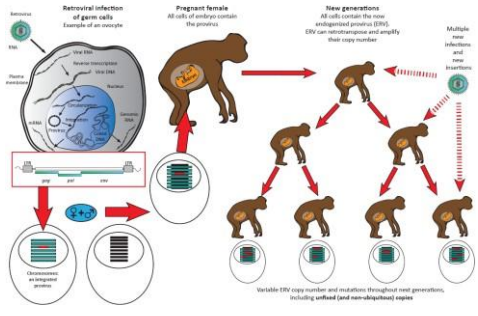
E. Premkumar Reddy, Magnhild Sandberg-Wollheim, Richard V. Mettus, Phillip E. Ray, Elaine DeFreitas, Hilary Koprowski

Animal models: Some viruses capable of producing demyelination

- JMH strain of mouse hepatitis virus
- Theiler's infection of mice
- Visna virus of sheep
- Canine distemper
- Measles
- Mumps
- Influenza
- Papovaviruses
- Herpes simplex virus
- HIV
- Togaviruses

Human endogenous retroviruses (HERVs)

- sequences belonging to human ERV families retaining structural features of retroviral genomes that have become integrated into the genome through repeated infections during evolution.



Endogenous Retroviruses

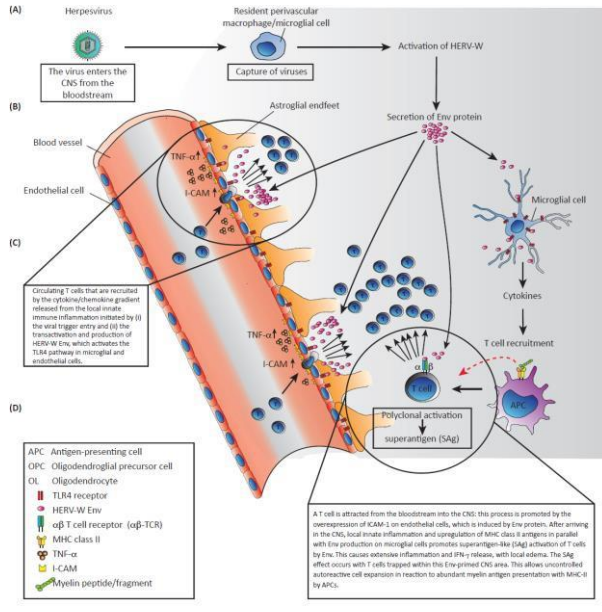
- The eukaryotic genome is composed of DNA sequences, many derive from mobile genetic elements estimated to account for about 50% of the entire human genome.
- There are 31 different families of HERVs that together make up about 8% of the human genome, four times more DNA than is devoted to protein coding genes
- HERV-W makes up about 1% of the human genome and is part of a superfamily of repetitive and transposable elements.

Silent HERVs can be activated by environmental riggers

- DNA methylation & histone modification are essential to epigenetic control of human genes, HERV including.
- HERVs activation is linked to chromatin state.
- The baseline predisposition of a HERV copy to be activated can be tissue, cell, or maturation stage-specific.
- Inflammatory stimuli may activate HERVs via epigenetic dysregulation such as proinflammatory cytokines that act in cultured cells from MS patients

EBV

- The most consistent and independently confirmed studies are for EBV by
  - history of infectious mononucleosis
  - high anti-EBNA-1 (EBV nuclear antigen 1) IgG titers before MS onset.
- EBV is known to activate HERV-W/MSRV *in vitro* and *in vivo*.
- Thus, EBV could be an initial trigger, while HERV-W/MSRV is a direct neuropathogenic contributor, before and during MS, in addition to its known contribution to promoting autoreactive T cells, immunoinflammation, and remyelination blockade.



Involving HERV-W activation and envelope (Env) protein expression triggered by an environmental factor.

This causes dysregulated inflammatory and immune responses accompanied by activation of microglial cells, which thereby also express pathogenic HERV-W Env protein.

transcription of HERV genes and/or reverse transcriptase (RT) activity is increased by HSV-1, VZV, CMV, HHV-6 and EBV

Additional triggers besides EBV

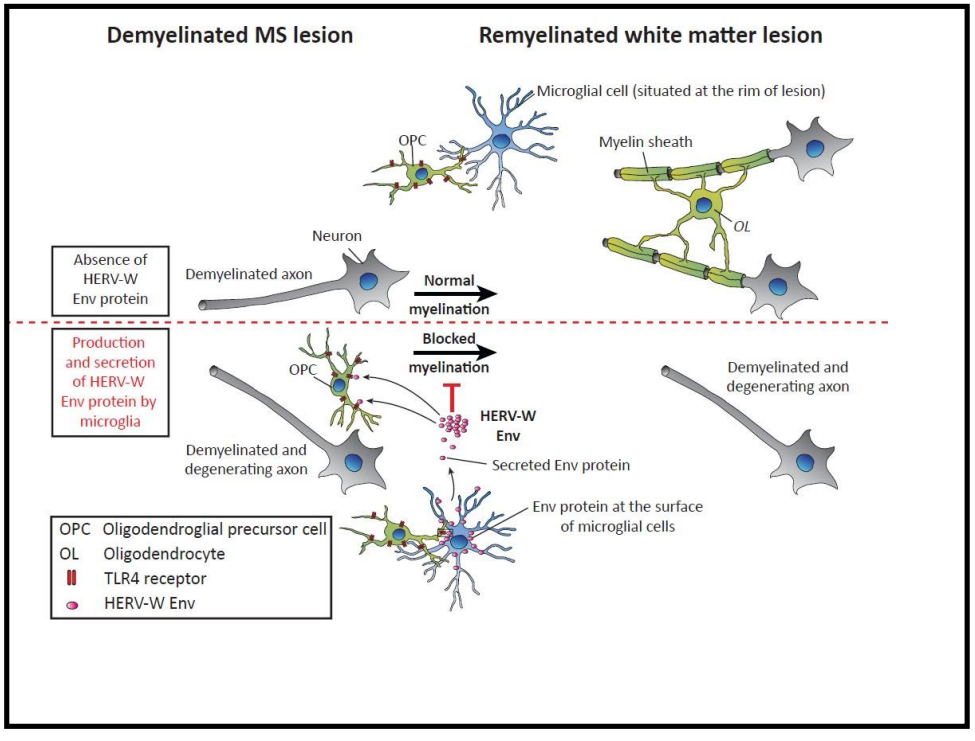
- Herpesviridae are now suggested to upregulate HERV-W expression, with its Env protein acting as a pathogenic effector in MS.
- HERVs express pathogenic proteins in disease, and the best evidence of an association and pathogenic involvement is for HERV-W/MSRV (detected in MS blood, spinal fluid, and brain, in parallel with MS stages, active/remission phases, and therapy outcome).
- Other viruses reported to transactivate HERVs are the exogenous retroviruses HTLV-1 and HIV-1

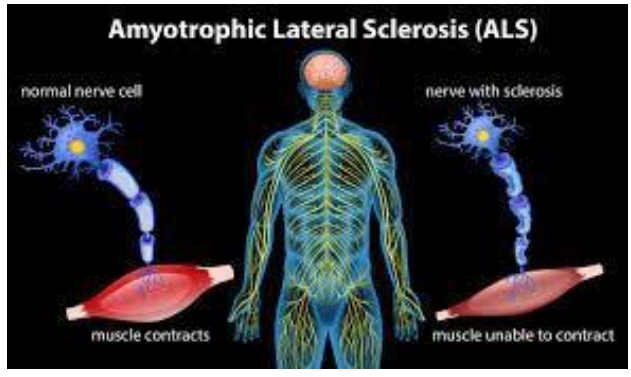
Mechanisms of activation

- If HERV proteins are not expressed, HERV RNA expression (transcription alone) does not seem to have biological effects per se in humans.
- When produced, HERV proteins are not implicitly pathogenic.
- HERV H, K, W are abnormally represented in MS

Therapy

- There is correlation between serum levels of HERV-W proteins (Env) and MS activity to suggest that it might be used as a therapeutic target in MS.
- A one year study phase IIb with a monoclonal antibody directed against Env in 260 RRMS patients is now on going





HERV-K and ALS

- HERV-K is so-named because it uses lysine (K) tRNA as a primer
- 11 largely complete proviral sequences have been identified in human genomes
- Some endogenized HERV-K elements have complete ORFs and can form complete viral particles
- It is unknown if expression of HERV-K in ALS patients derives from a single complete retroviral sequence or represent trans-complementation between partially defective complementary copies.

ALS & Retroviruses

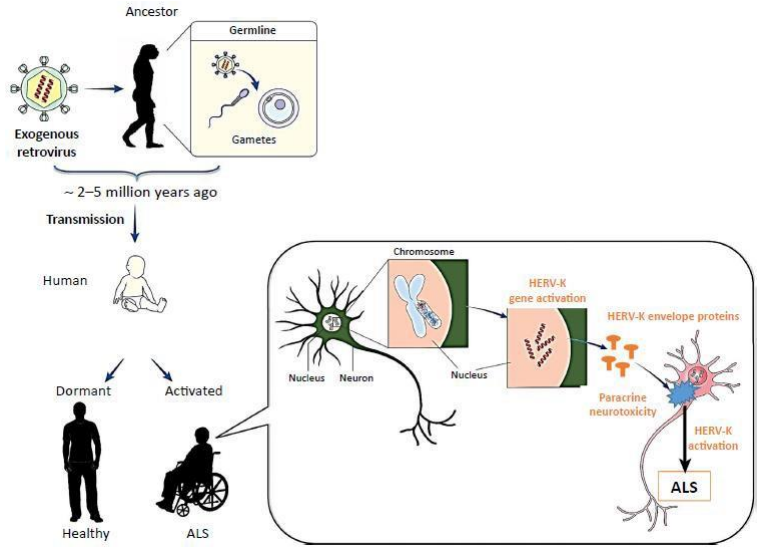
- The first evidence that retroviral elements might be activated in ALS came from a study where brain tissues from two ALS patients in Guam were found to have RNA-directed DNA polymerase activity.
- The activity was RNase-sensitive suggesting RT activity.
- Studies in ALS patients confirmed the presence of RT in serum and showed that nearly 50% of the patients have detectable RT activity.
- However, attempts to find an exogenous retrovirus in ALS patients were unsuccessful and no virus or transmissible agent was identified.

ALS & Retroviruses

- The fact that HERVs in ALS arise from the genome and not from the environment might explain why RT was detected in ALS brain and blood samples, but no human-to-animal or human-to-human transmission of the disease was documented.
- RT encoded by the pol gene of HERV-K reported in the brain of sporadic ALS patients was specific for ALS
- Expression levels of HERV-K pol, env, and gag genes in brains of sporadic ALS patients correlated with each other, suggesting that an entire HERV-K genome is activated

HERV-K & ALS

- If HERV-K expression is forced in neurons, it causes cellular degeneration mediated by its Env protein.
- Transgenic mice expressing HERV-K Env in neurons develope a clinical & pathological phenotype that resembles ALS, with upper and lower motor neuron degeneration
- What triggers HERV-K expression in adult neurons of ALS patients remains unknown.



Antiretroviral therapy

- An approach similar to that taken for HIV could be considered
- A panel of antiretroviral drugs approved for treating HIV infection was screened, but elevated concentrations were found to be necessary to control HERV-K replication in HeLa cells *in vitro*
- A pilot clinical trial with indinavir, a protease inhibitor used for HIV, failed to show any efficacy in ALS

Antiretroviral therapy

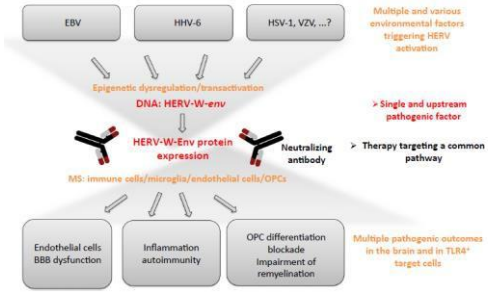
- Some patients with HIV infection can develop an ALS-like syndrome, which may show symptom regression and halted evolution under treatment with anti-HIV drugs
- These patients also have expression of HERV-K in blood, with levels that fell after antiretroviral drugs therapy
- It is possible that anti-HIV drugs might indeed inhibit HERV-K, but that their efficacy is not as good as for HIV

Open trial

An open-label pilot study has been initiated in Australia and the UK. The trial is enrolling 40 patients with ALS, and will follow them for 3 months without treatment; then treat them for 6 months with triumeq – which includes two reverse transcriptase inhibitors (abacavir and amivudine) that have been shown to effectively inhibit HERV-K RTactivity *in vitro*, and an integrase inhibitor dolutegravir

Therapeutic options for MS & ALS

- To test antiretroviral drugs
- To use a humanized neutralizing antibody targeting the toxic Env protein that mediates HERV-W pathogenicity



Take home messages

- HERVs are evolutionarily acquired, mostly defective and inactive, and are epigenetically silenced genetic elements.
- They might have pathogenetic significance in neurological diseases.
- How can we neutralize HERV endogenous proteins is a major therapeutic challenge. Potential approaches include vaccination, antibody-mediated neutralization of pathogenic components, and antiretroviral compounds.