From first retroviral detection in Multiple Sclerosis (MSRV) to the human endogenous retrovirus type W family (HERV-W), the association with disease and the identification of env-encoded pathogenic effector as a therapeutic target in in vitro and in vivo models.

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The first observation of retrovirus-like particles with reverse transcriptase activity in multiple sclerosis (MS) was made in leptomeningeal cells shed in the cerebrospinal fluid of a patient with progressive MS (Perron, Geny et al. 1989). It was thereafter replicated in series of macrophage cultures and in EBV-transformed B-cells from MS versus controls by the same (Perron, Lalande et al. 1991) and other independent groups (Haahr, Sommerlund et al. 1991; Serra, Sotgiu et al. 2001). The molecular identification of this "MS-associated" retrovirus (MSRV) RNA was achieved from purified virions with specific buoyant density and reverse transcriptase activity on sucrose gradients, representing different isolates concentrated from litres of culture supernatant of leptomeningeal or EBV-transformed cells from MS versus mock controls (Perron, Garson et al. 1997). Sequences of a complete retroviral genome were obtained by PCR extension to all retroviral genes in similarly purified particles (Komurian-Pradel, Paranhos-Baccala et al. 1999) and unravelled the previously unknown HERV-W family (Blond, Beseme et al. 1999). Thus, a novel human retrovirus was discovered but did not correspond to the expected HTLV-like retrovirus (Koprowski, DeFreitas et al. 1985). It corresponded to the poorly understood category of Human endogenous retroviral elements (HERVs), which entered the germline after the speciation of old world monkeys about 25 million years ago (Voisset, Blancher et al. 1999) and were still considered as "junk DNA" in the human genome.

The question then arose whether this expression was a consequence of the disease representing a trivial activation of harmless HERV elements or, whether this could be pathogenic and be involved in MS pathogeny. Moreover, this question acquired a new dimension when the human genome sequencing later revealed that HERVs represented about 8% of our genome.

Therefore, different aspects were explored and results of successive studies with independent confirmations provided answers that have now depicted a central pathogenic role of HERV-W envelope protein (MSRV-Env or HERV-W/Env) in the initiation and lifelong holding of MS pathogeny. They have also evidenced that this HERV-W activation, along with its envelope protein production, was a common pathogenic pathway in several other neuroinflammatory or autoimmune diseases.

An overview of the key aspects that were elucidated and allowed to bridge this original discovery to the clinical relevance and to an innovative therapeutic development will be presented. After early isolations of cell cultures expressing specific HERV-W elements with characteristics of retroviruses in MS, (i) their activation by particular infectious agents from the environment, (ii) the detection of HERV-W envelope (Env) and other proteins with elevated RNA expression in patient's lesions or in their blood, (iii) the evidence of Env-mediated pathogenic pathways through TLR4 receptors in different targeted cells and (iv) the induction of animal models for MS or for other associated diseases using injections of recombinant Env protein or transgenic mice expressing HERV-W/MSRV-env gene, will be reviewed and discussed. Details of each of these aspects, enriched with recent and novel discoveries, will be described in other dedicated presentations. An up-to-date knowledge on the physiopathology of HERV-W expression in MS and in other diseases, as well as on the validation of the therapeutic target along with the anti-Env humanized antibody presently in clinical development for MS, will be provided.

Altogether, the present data now suggest that HERV elements could be missing links between environmental factors and the pathogenic processes of complex human diseases, in which the final physiopahological consequences have no validated etiological explanation. Thus, such "dormant retroviruses awaken" have been designated as "the enemy within" (Engel and Hiebert 2010) and may constitute a different category of pathogens from classical environmental and infectious microbes, since arising from the host's genome itself.

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