Cell Mol Neurobiol (2014) 34:1087–1096
DOI 10.1007/s10571-014-0100-7

REVIEW PAPER

The Retrovirus/Superantigen Hypothesis of Multiple Sclerosis

Alexander Emmer · Martin S. Staege · Malte E. Kornhuber

Received: 11 June 2014 / Accepted: 9 August 2014 / Published online: 20 August 2014

Abstract The pathogenesis of multiple sclerosis (MS) is as yet unknown. Commonly, MS is assumed to be due to an autoimmune inflammation of the central nervous system (CNS). Neurodegeneration is regarded to be a secondary reaction. This concept is increasingly being challenged. Human endogenous retroviruses (HERV) that could be locally activated in the CNS have been proposed as an alternative concept. HERV-encoded envelope proteins (env) can act as strong immune stimulators (superantigens). Thus, slow disease progression following neurodegeneration might be induced by re-activation of HERV expression directly, while relapses in parallel to inflammation might be secondary to the expression of HERV-encoded superantigens. It has been shown previously that T-cell superantigens are capable to induce a cellular inflammatory reaction in the CNS of experimental animals similar to that in MS. Furthermore, B-cell superantigens have been shown to activate blood leucocytes in vitro to produce immunoglobulin in an oligoclonal manner. It remains to be established, whether the outlined hypothesis accords with all known features of MS. Furthermore, anti-HERV agents may be taken into consideration to enrich and improve MS therapy.

Keywords Human endogenous retrovirus (HERV) · Envelope protein · Superantigen · Multiple sclerosis · Pathogenesis · Therapy

A. Emmer (✉) · M. E. Kornhuber
Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
e-mail: alexander.emmer@uk-halle.de

M. S. Staege
Department of Pediatrics, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

The Autoimmune Concept of Multiple Sclerosis

Multiple sclerosis (MS) is a neurodegenerative disease with unresolved pathogenesis. Up to now, an autoimmune attack against myelin autoantigens is considered to be the primary and main event in the pathogenesis of MS (Hemmer et al. 2003; Pender and Greer 2007). Molecular mimicry has been considered to be the potential trigger for central nervous system (CNS) autoimmunity (Chastain and Miller 2012). The anti-inflammatory therapeutic approach is in line with these assumptions (Hohlfeld and Wekerle 2004; Steinman 2007). It is presumed that the immune therapy is able to prevent secondary neurodegeneration. Therefore, an early onset of immune-directed therapy has been recommended (Coyle and Hartung 2002; Hartung et al. 2005).

Paradigm Shift

Recently, the autoimmune concept for MS pathogenesis has been challenged from different directions: (i) Despite multiple attempts to substantiate a role of myelin autoantigens in MS, no unequivocal proof has been supplied for this idea. In fact, T-cells that specifically recognize peptides of myelin proteins have been shown to be equally present in healthy subjects and in MS patients (Pette et al. 1990; Holmøy 2007). Evidence is also lacking for the hypothesis that a defective immune regulation would play a role in MS (Goverman 2009). (ii) Several lines of evidence suggest that inflammation in MS could be a secondary phenomenon. No immune cells have been found by histopathology in developing MS lesions at the onset of an MS relapse (Barnett and Prineas 2004). The latter finding has been limited to few cases that had been available for pathological analysis. It has been discussed, however, that

the MS plaque may be subjected to some kind of metamorphosis (Kornhuber 2006) with inflammation as a secondary event: 3 months prior to the onset of contrast enhancement, subtle but significant alterations take place at the plaque site in the brain tissue as detected by magnetization transfer imaging (Filippi et al. 1998). As contrast enhancement is taken as a correlate of inflammation (Smith et al. 1993), it seems to be likely, that non-inflammatory events occur within the MS plaque before immune cells come into play. In contrast, inflammation parameters in the blood display quite a different time course. They rise within a few weeks before the acute attack (Beck et al. 1988). This rise could be due to various types of systemic infections, which are well known to contribute to an acute attack (Correale et al. 2006). Lesion metamorphosis would also be in line with different types of plaques that have been detected by histopathology (Lucchinetti et al. 2000). Thus, different types of MS need not necessarily be taken into consideration to explain this phenomenon. In fact, the postulation of diverse separate subtypes of MS disagrees with the results of epidemiologic studies which suggest that all known clinical subtypes are part of one and the same disease process (Confavreux and Vukusic 2006a). A primary neurodegenerative process would also fit the finding that 20 % of the axons in the cerebral white matter have been lost already when MS is diagnosed. *N*-acetyl-aspartic acid has been shown to be significantly reduced in the cerebral white matter of MS patients with early disease compared to control subjects by magnetic resonance spectroscopy (De Stefano et al. 2002; Filippi et al. 2003). This diffuse axonal loss can hardly be attributed to the few MS lesions that are commonly present on magnetic resonance images in this early state of the disease (De Stefano et al. 2002; Filippi et al. 2003). In addition, axonal loss and demyelination have been demonstrated to progressively decrease irrespective of an ongoing immunomodulatory therapy (Anlar et al. 2003; Parry et al. 2003).

Immune Therapy and Progression of the Disease

Excess mortality of patients with MS as compared with the general population has declined significantly since 1950 (Llorca et al. 2005, Brønnum-Hansen et al. 2006). An influence of immune therapy on this phenomenon has not yet been unequivocally established, and there may be further factors of influence such as improvements of economic status and general health care including symptomatic MS treatment. Provided that inflammation is the driving force of the disease, disability would follow the inflammatory activity. Such correlations are weak at best, and not given when the disease progresses steadily (Confavreux et al. 2003). Moreover, the inflammatory activity in MS does not exert a detectable influence on the ongoing process of cerebral atrophy (Cheriyan et al. 2012). It is common knowledge that MS patients with a progressive course from onset do not benefit from any immunomodulatory therapy. Actually, the impact of immune modulation in MS segregates into a moderate effect on relapses and a lacking or at most weak effect on disease progression (Kornhuber et al. 2005). Accordingly, it has been shown, that a longer lasting therapy with interferon beta has no influence on disability, neither in patients with a relapsing-remitting type of disease (Confavreux and Vukusic 2006b; Shirani et al. 2012), nor in patients with secondary progression (Confavreux and Vukusic 2006b; La Mantia et al. 2012). This finding has been attributed by some authors to the relatively short study periods or to imprecise clinical scales (Hohlfeld 2012). However, if MS is considered to be a primary neurodegenerative disease, the failure of immune therapy is consistent.

Alternative Hypothesis: HERV/Superantigen Pathogenesis

In our eyes, the hypothesis of MS as a primary autoimmune disease is hardly tenable any more. Therefore, alternative concepts have to be developed that better fit the real findings in MS patients that have been gathered over the last decades. Actually, simple and attractive views in agreement with the dualism of degeneration and inflammation in MS are already available: A clear and reproducible association of human endogenous retroviruses (HERVs) in MS-patients has been shown previously (for review see e.g., Perron and Lang 2010; Nexø et al. 2011). In 1989, Perron and coworkers detected retroviral activity in an MS patient (Perron et al. 1989). Consequently, the concept of an MS-associated retrovirus (MSRV) has been developed (Perron et al. 1997). Today, of the more than 30 HERV-families, few have been considered to be associated with MS (Perron and Lang 2010; Christensen 2010; Nexø et al. 2011; Tai et al. 2008).

At least 8 % of the human genome is composed of endogenous retroviral sequences. These sequences were integrated into the human genome in the course of the evolution and are now transmitted from generation to generation like other genes. Some of these sequences are involved in normal physiological functions (Dupressoir et al. 2012). HERVs have been found to be associated with different diseases, e.g., endogenous psychoses, psoriasis, diabetes mellitus type 1, rheumatoid arthritis and diverse malignant tumors (Dolei 2006; Balada et al. 2009). The majority of HERVs integrated in our genome is not competent to replicate and most HERV sequences are presumably silent. Thus, harmful properties of HERVs

Table 1 Activators of HERV expression

Factor	Endogenous retrovirus	Model	References
Azacytidine	HERV-K	Melanoma cell lines	Stengel et al. (2010)
Aspirin	HERV-W	Neuroblastoma cell line	Liu et al. (2013)
Caffeine	HERV-W	Neuroblastoma cell line	Liu et al. (2013)
Epstein Barr virus—CD21 interaction	HERV-K18	Resting B cells	Hsiao et al. (2006)
Epstein Barr virus LMP2A	HERV-K18; HERV-K18	Lymphoblastoid cell lines, Burkitt lymphoma cell lines; HERV-K18-transgenic murine B cell lymphoma cell line	Sutkowski et al. (2004), Hsiao et al. (2009)
Glial cell missing 1	HERV-W	Choriocarcinoma cell lines	Yu et al. (2002)
Herpes Simplex virus 1	HERV-K; HERV-W	Teratocarcinoma cell lines; Neuroblastoma cell line, SV40 large T antigen-transformed brain microvasculature endothelial cells	Kwun et al. (2002), Ruprecht et al. (2006)
Human Cytomegalovirus	Multiple viruses	Varying cancer cell lines, endothelial cells, monocytes	Assinger et al. (2013)
Human Herpesvirus 6A	HERV-K18	T lymphoblastoid leukemia cell line	Tai et al. (2009)
Human Herpesvirus 6B	HERV-K18	Peripheral blood mononuclear cells	Turcanova et al. (2009)
Human Immunodeficiency virus 1 tat	HERV-K	Peripheral blood lymphocytes, T cell leukemia cell lines	Gonzalez-Hernandez et al. (2012)
Human T lymphotropic virus 1 tax	Multiple HERV	T cell leukemia cell line	Toufaily et al. (2011)
Hypoxia	HERV-R (ERV3)	Hodgkin's lymphoma cell lines	Kewitz and Staege (2013)
Influenza A virus	HERV-W	Tumor cell lines, primary fibroblast cultures	Li et al. (2014)
Ionizing radiation	HERV-R (ERV3)	Embryonic kidney cell line, Keratinocyte cell line	Lee et al. (2012)
Microphthalmia-associated transcription factor M	HERV-K	Melanoma cell lines, Embryonic kidney cell line	Katoh et al. (2011)
PPARgamma signaling	HERV-W	Primary cytotrophoblast cultures, Choriocarcinoma cell lines	Ruebner et al. (2012)
Retinoic acid	HERV-W	Primary cytotrophoblast cultures, Choriocarcinoma cell lines	Ruebner et al. (2012)
Toxoplasma gondii	Multiple HERV	Ewing sarcoma cell lines	Frank et al. (2006)
Tumor necrosis factor alpha	HERV-W	Glioma cell line	Mameli et al. (2007)
Ultraviolet B	Multiple HERV; HERV-K	Primary keratinocytes, Keratinocyte cell line; Melanoma cell lines	Hohenadl et al. (1999), Schanab et al. (2011)

possibly depend on the circumstances and the organ in which they are expressed. In comparison to healthy individuals, MS patients have been shown to display genetic differences in the promoter region of HERV-Fc1 (Nexø et al. 2011). Such differences might contribute to the differential expression of HERVs in MS patients as compared with healthy subjects (Nexø et al. 2011). Other factors have been reported to influence HERV expression (Table 1). For example, estradiol primes human breast cancer cells for subsequent progesterone-induced HERV-K expression (Ono et al. 1987). Similarily, it was shown that HERV expression in keratinocytes increases under the influence of UV light (Hohenadl et al. 1999). Due to the impact of endogenous and exogenous factors in MS, it would be worth to investigate further such factors (sexual hormones, light exposure) in the context of HERV expression. Environmental parameters could also play a role in regard to the distribution of MS prevalence in different geographical regions.

It is well known that the gammaherpesvirus Epstein Barr virus (EBV) plays a role in MS. Actually, MS has been shown to become manifest within a few years after EBV-infection (Levin et al. 2010). When HERVs are thought to be involved in the pathogenesis of MS, there should be

some link between EBV and HERV activation. Indeed, HERVs can be transactivated by herpes viruses including Herpes simplex virus 1, cytomegalovirus and EBV (Sutkowski et al. 2001; Nellåker et al. 2006; Assinger et al. 2013). The potent transactivating activity of HSV has been attributed to the HSV alpha gene product immediate early protein 0 (ICP0) (Everett 1984; Gelman and Silverstein 1985; O'Hare and Hayward 1985).

Furthermore, it was shown that ICP0 of HSV-1 transactivates the LTR-directed transcription of the human endogenous retrovirus K (Kwun et al. 2002). In addition to molecular mimicry and epitope spreading triggered by an excessive and prolonged immune stimulation, transactivation of HERVs by EBV and subsequent superantigenic stimulation of T cells might be involved in autoimmune phenomena (Dreyfus 2011). Transactivation by HSV-1 of the retrovirus of the LM7 cell line that was later termed MSRV has been shown as early as 1993 (Perron et al. 1993).

T-Cell Superantigens

If HERVs would play a causative role in MS, all MS features should fit into this scenario. First of all, a cellular inflammation takes place in MS plaques. Actually, gene products encoded by endogenous retrovirus sequences have been shown to induce clonal deletion of lymphocytes in a V-beta specific manner resembling that known for superantigens (SAgs) (MacDonald et al. 1988). It has been shown previously that the envelope protein of MSRV leads to polyclonal expansion of Vbeta16 T-lymphocytes in vitro (Perron et al. 2001). Furthermore, SCID-mice engrafted with human peripheral blood mononuclear cells intraperitoneally developed T-lymphocyte dependent brain hemorrhage albeit without encephalitis after i.p. injection of MSRV-virions (Firouzi et al. 2003). Of course, superantigens have been tested in the context of experimental autoimmune encephalomyelitis (EAE). However, controversial results have been presented with both, augmentation or attenuation of EAE (Rott et al. 1992; Perron et al. 2013). To test, if SAgs could induce inflammation similar to that in MS within central nervous tissue directly and not by the detour of EAE, we have previously used bacterial exotoxins (Kornhuber et al. 2002; Emmer et al. 2008, 2010). In healthy rodents without prior immune stimuli, SEA present locally within the brain does not induce a major inflammatory response (Kornhuber et al. 2002). The latter can be markedly amplified, however, after i.v.-injection of spleen cells that had been non-specifically activated by Concanavalin A (Kornhuber et al. 2002). Similarly, acute attacks in MS could be triggered by non-specific immune stimuli i.e., stress or infectious diseases. Interestingly, CD8-positive T-cells dominate the SEA-driven perivascular round cell reaction (Emmer et al. 2010). This type of lymphocyte has been found to predominate also in inflammatory MS lesions (Friese and Fugger 2009). The oligoclonal expansion of T-cells in the cerebral tissue of MS patients (Junker et al. 2007) appears to accord to a superantigenic stimulus. Furthermore, inflammation is detectable in non-myelinated areas such as the retina. While this finding is well in accord with a superantigenic stimulus, it would not be expected when a myelin autoantigen is involved in the MS pathogenesis. Again, no separate disease entity can be proposed based on whether the retina is involved or not in MS patients. Thus, it has been shown, that MS patients with or without retinal involvement do not show any differences (Schmidt et al. 2001).

B-Cell Superantigens

Beside cellular inflammation, a humoral immune reaction is an essential feature of MS: oligoclonal bands (OCB) can be detected in over 90 % of MS-patients by isoelectric focusing in the cerebrospinal fluid. It has been reported, that only 1 % of these OCB contain antibodies that are directed against CNS antigens (Kaiser et al. 1997; Owens et al. 2009). In contrast, the spectrum of antigen specificities that is present in OCB is so diverse, that the term "nonsense antibodies" has been used for this phenomenon (Mattson et al. 1980). If SAgs play a role in the pathogenesis of MS, evidence should be presented that OCB may be induced by them. In fact, preliminary results support the notion, that B-cell SAgs can induce OCB in in vitro cultures of peripheral blood leukocytes from human blood donors (Emmer et al. 2011). Thereby, the envelope glycoprotein 120 (gp120) of human immunodeficiency virus (HIV) was capable to activate blood leukocytes to form antibodies against unrelated antigens including Measles virus, Varicella-zoster virus and Rubella virus (Emmer et al. 2011).

Antigen-Presentation

As far as we can see, the effects of HERV-encoded envelope proteins have not been studied in the context of cerebral antigen presenting cells (APCs) such as microglial cells or astrocytes or eventually also monocytes or dendritic cells (DC) that may enter the CNS during states of inflammation (D'Agostino et al. 2012). Nevertheless, interactions of conventional SAgs such as e.g., Staphyloccal enterotoxins or toxic shock syndrome toxin-1 (TSST-1) with different APCs have been reported.

For cerebral APCs only few studies are available so far. Treatment of primary microglia with purified Staphylococcal enterotoxin B (SEB) has been shown to augment the TNF-α production in response to the TLR2 ligand Pam3-Cys (Vidlak et al. 2011). SEB and TSST-1 have been reported to bind with high affinity to MHC class II antigen expressing astrocytes (Hassan-Zahraee et al. 2000). Contrasting results have, however, been reported by Rott et al. (1993).

Toxic shock syndrome toxin-1 (TSST-1) has been shown to potently induce IL-1 in human monocytes (Ikejima et al. 1984; Parsonnet et al. 1986). SEA, SEB, and TSST-1 were shown to activate and induce IL6 in peritoneal macrophages from lipopolysaccharide-responsive C3HeB/FeJ mice (Fleming et al. 1991). Furthermore, SEB and TSST-1 have been demonstrated to induce IL-1 and TNF secretion in human monocytes and monocytic cell lines (Trede et al. 1991). Eventually, the activation of monocytes by TSST-1 is mediated by tyrosine phosphorylation (Scholl et al. 1992). The maturation process that has been induced by systemic administration of SEB was shown to be accompanied by upregulation of CD40, CD80 and CD86 expression in splenic interdigitating dendritic cells (IDCs) but not in other APCs such as macrophages and B cells (Yoon et al. 2001). Beside the known binding of SAgs by MHC class II molecules on the surface of APCs, SAgs have been demonstrated to be taken up in DCs by transportation and trafficking (Ganem et al. 2013). It has been speculated that this SAg uptake might increase the local SAg concentration and thus enhance their presentation on the cell surface, e.g., to lymphocytes (Ganem et al. 2013). Furthermore, SAgs up-regulate monocyte surface toll-like receptor (TLR) 2 and TLR 4 expression through MHC class II signaling (Hopkins et al. 2005, 2008). The SAg SEC1 has been suggested to play a role in the differentiation of bovine peripheral blood mononuclear cells into DC (Seo et al. 2009).

Beside stimulatory effects on APCs, SAgs have been shown to lead to APC apoptosis. Thus, SEB was shown to selectively increase the number of apoptotic CD80(−) monocytes, presumably via CD95 dependend pathway (Takahashi et al. 2001). Furthermore, a significant depletion of Langerhans cells has been reported to be induced by SEA or exfoliative toxin but not by TSST-1 (Pickard et al. 1994).

From the above cited reports it becomes apparent that the interaction of SAgs locally expressed in the brain such as HERV-encoded envelope proteins might lead to the activation of cerebral APCs. In fact such activated APCs such as microglial cells are typically seen in the context of widespread demyelination of cerebral tissue of MS patients (Lassmann 2013). By way of contrast, microglia has been found to be not or at most mildly activated during the course of EAE (Vainchtein et al. 2014). Furthermore, the SAg–APC interaction might lead to the liberation of cytokines such as IL1, IL6, and TNF-α. This in turn could lead to reactions of the cerebral endothelial cells and to enhanced recruitment of immune effector cells, i.e., to the initiation of an inflammatory response.

Superantigens and HLA-Association

In MS patients, certain HLA-types have been shown to be significantly more common than in the general population (Ramagopalan et al. 2009). This HLA-association is complex and does hardly allow any conclusion with respect to the cause of the disease. Like other antigens, T-cell-SAgs bind to HLA-molecules which present them to the T-cell receptor in a Vβ-dependent manner. If a role for HERV-encoded SAgs is assumed within the MS pathogenesis, then differences in the HLA-association should be present between patients with a relapsing-remitting type of course and those who show slow progression from the disease onset. Actually, such differences have been repeatedly found (Madigand et al. 1982; Van Lambalgen et al. 1986; Francis et al. 1987; Olerup et al. 1989). Furthermore, an association between the HLA-type and the disease course could be expected especially in those patients who actually show signs of inflammation in form of relapses, and who respond to immune modulating therapy. Contradictory results have been reported regarding this issue. Nevertheless, as a reproducible finding that may hint in this direction, the manifestation age of MS depends on the presence of the HLA DRB1*15:01 allele (Masterman et al. 2000; Sawcer et al. 2011). If the HLA DRB1*15:01 allele is absent, MS becomes manifest at a higher age. If this relation holds true, it could be that the different types of MS course form a continuum in which patients with a primary type of course from onset would experience their first relapse at an advanced age. In this case, it would be difficult to distinguish with certainty a relapse from the ongoing disease process.

HERV and Neurodegeneration

How could primary degeneration in the CNS agree with a HERV-pathogenesis? Oligodendrocyte apoptosis has been detected in MS plaques in an early plaque stage with immune reactivity against caspase 3 (Prineas and Parratt 2012). Apoptosis of oligodendrocytes has been described in the context of diverse viral diseases, e.g., in progressive multi-focal leukoencephalopathy in JC-virus infection (Merabova et al. 2008). Furthermore, axonal loss and demyelinisation is a feature of HIV-encephalopathy (Bell

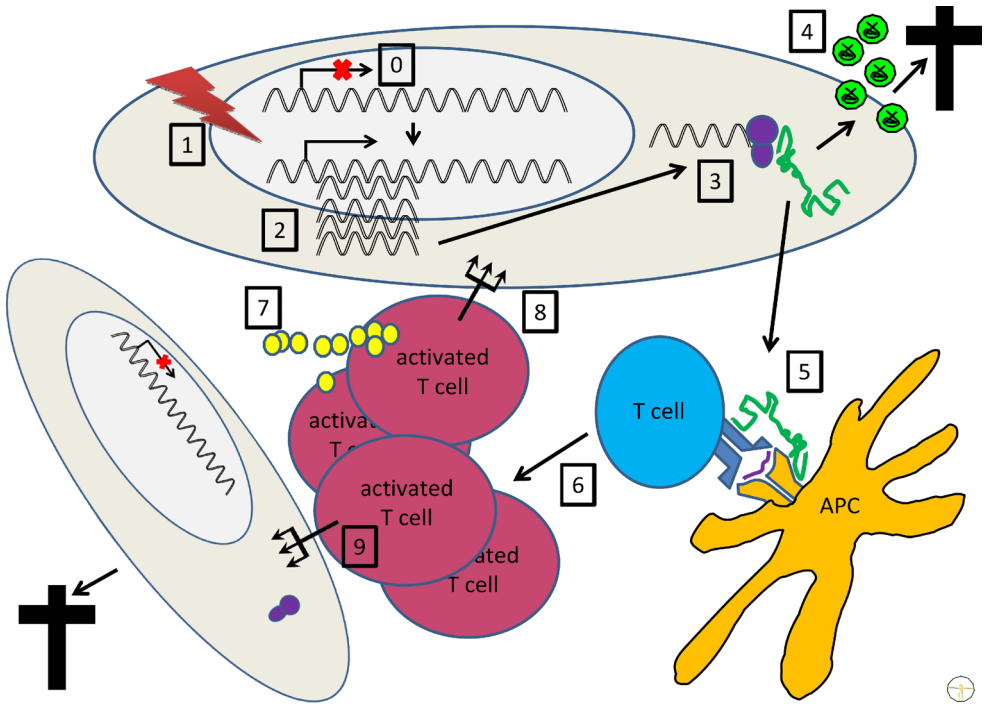

Fig. 1 A model for HERV/superantigen mediated neurodegeneration and neuroinflammation. HERVs constitute an integral part of our genome. Under normal conditions, expression of HERVs is switched off epigenetically (*0*). Triggered by diverse factors (see Table 1), reactivation of HERVs expression can be induced (*1*). The majority of HERV-encoded RNAs contain point mutations and deletions that hinder synthesis of HERV-encoded proteins. Such RNAs might be involved in dysregulation of RNA metabolism (*2*). HERV-encoded RNAs with intact open reading frames can be translated into proteins (*3*). In rare cases, complete virions can be formed (*4*) which might have direct cytopathic effect. In addition, single proteins can act as antigens or superantigens for T cell stimulation (*5*). Such superantigens can lead to depletion of V beta families but also to activation of proliferation of oligoclonal T cells (*6*). Activated T cells secrete cytokines which can lead to immune dysregulation (*7*). In addition, activated T cells might be able to interact and kill other cells including the superantigen expressing cells (*8*). However, bystander cell killing can be independent from the expression of the superantigen which was responsible for the induction of the immune response (*9*)

1998). Certain proteins of HIV may induce apoptosis markers like caspase 3 or TUNEL (Hauser et al. 2009). Overexpression of the HERV-W env has been reported to be associated with elevated levels of small conductance Ca(2+)-activated K(+) channel protein 3 (SK3) in human neuroblastoma cells. This finding has been discussed in the context of neuronal excitotoxicity (Li et al. 2013). These findings suggest that other retroviruses, eventually including HERVs might be capable to induce degeneration of oligodendrocytes or axons, too. Indeed, cytotoxic effects of HERV products on oligodendrocytes have been described (Antony et al. 2004; Kremer et al. 2013). In addition to a direct cytopathic effect of HERV, SAg-activated T cells might be able to destroy bystander cells. Under certain circumstances, strong activation of T cells can induce non-HLA restricted cytotoxic activity against innocent bystander cells (Dick et al. 1993; Staege et al. 1996, 1998, 2000, 2003). Such bystander lysis could contribute to secondary neurodegeneration.

Despite the fact that many researches stick to EAE as their favorite model for MS, the concept of MS as an autoimmune disease driven by anti-myelin autoantigenic mechanisms is hardly tenable any more. Alternatively, a key role in MS pathogenesis might be played by HERVs that are not safely silenced. In fact, such HERVs have been shown to become locally activated in the CNS of MS patients. In this context, it is not far to speculate that HERV-encoded envelope proteins act as SAgs and thereby cause a cerebral inflammatory reaction as has been established for bacterial SAgs already. Notably, the super-stimulatory effects would be expected to concern both, T-cells (inflammatory plaques) and B-cells (oligoclonal bands). Which consequences for MS therapy evolve, if a HERV/SAg pathogenesis is taken into account? (i) If MS is caused by HERVs, immune suppression or modulation can hardly be expected to influence slow disease progression. (ii) A substantial attenuation of neurodegeneration would require effective suppression of HERV-activation. (iii) It is readily explicable that immune therapy can reduce the rate and severity of relapses, while disease progression is hardly influenced. (iv) The extensive and expensive use of immune modulating therapies from the disease onset without taking the disease dynamics and

progression characteristics into account seems to be questionable (Fig. 1). (v) The development of ever new immune modulators does not warrant the necessary progress in the sense to avoid disability on the long term. By way of contrast, to develop mechanisms of silencing HERV expression poses an attractive base for a future therapy of this disabilitating disease. If in turn efficacy of such a therapy could be proven in progressive forms of MS, this would strongly support a HERV driven pathogenesis.

Acknowledgments A. E. and M. S. S. are supported by the Wilhelm-Roux program (FKZ 21/22, FKZ 25/28, and FKZ 25/22) of the University of Halle-Wittenberg. Furthermore, we gratefully acknowledge generous support by Novartis Pharma GmbH.

References

Anlar O, Kisli M, Tombul T, Ozbek H (2003) Visual evoked potentials in multiple sclerosis before and after two years of interferon therapy. Int J Neurosci 113:483–489

Antony JM, van Marle G, Opii W, Butterfield DA, Mallet F, Yong VW, Wallace JL, Deacon RM, Warren K, Power C (2004) Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. Nat Neurosci 7:1088–1095

Assinger A, Yaiw KC, Göttesdorfer I, Leib-Mösch C, Söderberg-Nauclér C (2013) Human cytomegalovirus (HCMV) induces human endogenous retrovirus (HERV) transcription. Retrovirology 10:132. doi:10.1186/1742-4690-10-132

Balada E, Ordi-Ros J, Vilardell-Tarrés M (2009) Molecular mechanisms mediated by human endogenous retroviruses (HERVs) in autoimmunity. Rev Med Virol 19:273–286

Barnett MH, Prineas JW (2004) Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol 55:458–468

Beck J, Rondot P, Catinot L, Falcoff E, Kirchner H, Wietzerbin J (1988) Increased production of interferon gamma and tumor necrosis factor precedes clinical manifestation in multiple sclerosis: do cytokines trigger off exacerbations? Acta Neurol Scand 78:318–323

Bell JE (1998) The neuropathology of adult HIV infection. Rev Neurol (Paris) 154:816–829

Brønnum-Hansen H, Stenager E, Hansen T, Koch-Henriksen H (2006) Survival and mortality rates among Danes with MS. Int MS J 13:66–71

Chastain EM, Miller SD (2012) Molecular mimicry as an inducing trigger for CNS autoimmune demyelinating disease. Immunol Rev 245:227–238

Cheriyan J, Kim S, Wolansky LJ, Cook SD, Cadavid D (2012) Impact of inflammation on brain volume in multiple sclerosis. Arch Neurol 69:82–88

Christensen T (2010) HERVs in neuropathogenesis. J Neuroimmune Pharmacol 5:326–335

Confavreux C, Vukusic S (2006a) Natural history of multiple sclerosis: a unifying concept. Brain 129:606–616

Confavreux C, Vukusic S (2006b) Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. Clin Neurol Neurosurg 108:327–332

Confavreux C, Vukusic S, Adelaine P (2003) Early clinical predictors and progression of irreversible disability in multiple sclerosis. Brain 126:770–782

Correale J, Fiol M, Gilmore W (2006) The risk of relapses in multiple sclerosis during systemic infections. Neurology 67:652–659

Coyle PK, Hartung HP (2002) Use of interferon beta in multiple sclerosis: rationale for early treatment and evidence for dose- and frequency-dependent effects on clinical response. Mult Scler 8:2–9

D'Agostino PM, Gottfried-Blackmore A, Anandasabapathy N, Bulloch K (2012) Brain dendritic cells: biology and pathology. Acta Neuropathol 124:599–614

De Stefano N, Narayanan S, Francis SJ, Smith S, Mortilla M, Tartaglia MC, Bartolozzi ML, Guidi L, Federico A, Arnold DL (2002) Diffuse axonal and tissue injury in patients with multiple sclerosis with low lesion load and no disability. Arch Neurol 59:1565–1571

Dick T, Staege MS, Reichmann G, Reske-Kunz AB (1993) Manifestation of the MHC-unrestricted killing potential of a cytotoxic T cell clone requires activation in response to MHC-restricted self-presentation of antigen. J Immunol 150:2575–2583

Dolei A (2006) Endogenous retroviruses and human disease. Expert Rev Clin Immunol 2:149–167

Dreyfus DH (2011) Autoimmune disease: a role for new anti-viral therapies? Autoimmun Rev 11:88–97

Dupressoir A, Lavialle C, Heidmann T (2012) From ancestral infectious retroviruses to bona fide cellular genes: role of the captured syncytins in placentation. Placenta 33:663–671

Emmer A, Gerlach K, Staege MS, Kornhuber ME (2008) Cerebral gene expression of superantigen encephalitis in the lewis rat induced by staphylococcal enterotoxin a. Scand J Immunol 67:464–472

Emmer A, Gerlach K, Staege MS, Kornhuber ME (2010) T-cell subsets of the encephalitis induced by the superantigen Staphylococcal Enterotoxin A (SEA) in the Lewis rat: an immunohistochemical investigation. Cell Immunol 264:93–96

Emmer A, Gerlach K, Staege MS, Kornhuber ME (2011) Superantigen-mediated encephalitis. In: Hayasaka D (ed) Pathogenesis of encephalitis. InTech, Rijeka, pp 213–234

Everett RD (1984) Trans-activation of transcription by herpes virus products: requirement for two HSV-1 immediate-early polypeptides for maximum activity. EMBO J 3:3135–3141

Filippi M, Rocca MA, Martino G, Horsfield MA, Comi G (1998) Magnetization transfer changes in the normal appearing white matter precede the appearance of enhancing lesions in patients with multiple sclerosis. Ann Neurol 43:809–814

Filippi M, Bozzali M, Rovaris M, Gonen O, Kesavadas C, Ghezzi A, Martinelli V, Grossman RI, Scotti G, Comi G, Falini A (2003) Evidence for widespread axonal damage at the earliest clinic stage of multiple sclerosis. Brain 126:433–437

Firouzi R, Rolland A, Michel M, Jouvin-Marche E, Hauw JJ, Malcus-Vocanson C, Lazarini F, Gebuhrer L, Seigneurin JM, Touraine JL, Sanhadji K, Marche PN, Perron H (2003) Multiple sclerosis-associated retrovirus particles cause T-lymphocyte-dependent death with brain hemorrhage in humanized SCID mice model. J Neurovirol 9:79–93

Fleming SD, Iandolo JJ, Chapes SK (1991) Murine macrophage activation by staphylococcal exotoxins. Infect Immun 59:4049–4055

Francis DA, Batchelor JR, McDonald WI, Hing SN, Dodi IA, Fielder AH, Hern JE, Downie AW (1987) Multiple sclerosis in north-east Scotland: an association with HLA DQw1. Brain 110:181–196

Frank O, Jones-Brando L, Leib-Mosch C, Yolken R, Seifarth W (2006) Altered transcriptional activity of human endogenous retroviruses in neuroepithelial cells after infection with Toxoplasma gondii. J Infect Dis 194:1447–1449

Friese MA, Fugger L (2009) Pathogenic CD8(+) T cells in multiple sclerosis. Ann Neurol 66:132–141

Ganem MB, De Marzi MC, Fernández-Lynch MJ, Jancic C, Vermeulen M, Geffner J, Mariuzza RA, Fernández MM, Malchiodi EL (2013) Uptake and intracellular trafficking of superantigens in dendritic cells. PLoS One 8:e66244

Gelman IH, Silverstein S (1985) Identification of immediate early genes from herpes simplex virus that transactivate the virus thymidine kinase gene. Proc Natl Acad Sci USA 82:5265–5269

Gonzalez-Hernandez MJ, Swanson MD, Contreras-Galindo R, Cookinham S, King SR, Noel RJ Jr, Kaplan MH, Markovitz DM (2012) Expression of human endogenous retrovirus type K (HML-2) is activated by the Tat protein of HIV-1. J Virol 86:7790–7805

Goverman J (2009) Autoimmune T cell responses in the central nervous system. Nat Rev Immunol 9:393–407

Hartung HP, Kieseier BC, Hemmer B (2005) Purely systemically active anti-inflammatory treatments are adequate to control multiple sclerosis. J Neurol 252:30–37

Hassan-Zahraee M, Ladiwala U, Lavoie PM, McCrea E, Sekaly RP, Owens T, Antel JP (2000) Superantigen presenting capacity of human astrocytes. J Neuroimmunol 102:131–136

Hauser KF, Hahn YK, Adjan VV, Zou S, Buch SK, Nath A, Bruce-Keller AJ, Knapp PE (2009) HIV-1 Tat and morphine have interactive effects on oligodendrocyte survival and morphology. Glia 57:194–206

Hemmer B, Kieseier B, Cepok S, Hartung HP (2003) New immunopathologic insights into multiple sclerosis. Curr Neurol Neurosci Rep 3:246–255

Hohenadl C, Germaier H, Walchner M, Hagenhofer M, Herrmann M, Stürzl M, Kind P, Hehlmann R, Erfle V, Leib-Mösch C (1999) Transcriptional activation of endogenous retroviral sequences in human epidermal keratinocytes by UVB irradiation. J Invest Dermatol 113:587–594

Hohlfeld R (2012) Multiple Sklerose: Verlangsamt Interferon-beta die Erkrankungsprogression? - Langzeiteffekt von IFN-ß auf Behinderungsprogression ist noch nicht belegt. Dtsch Med Wochenschr 137:2088

Hohlfeld R, Wekerle H (2004) Autoimmune concepts of multiple sclerosis as a basis for selective immunotherapy: from pipe dreams to (therapeutic) pipelines. Proc Natl Acad Sci USA 101:14599–14606

Holmøy T (2007) Immunopathogenesis of multiple sclerosis: concepts and controversies. Acta Neurol Scand Suppl 187:39–45

Hopkins PA, Fraser JD, Pridmore AC, Russell HH, Read RC, Sriskandan S (2005) Superantigen recognition by HLA class II on monocytes up-regulates toll-like receptor 4 and enhances proinflammatory responses to endotoxin. Blood 105:3655–3662

Hopkins PA, Pridmore AC, Ellmerich S, Fraser JD, Russell HH, Read RC, Sriskandan S (2008) Increased surface toll-like receptor 2 expression in superantigen shock. Crit Care Med 36:1267–1276

Hsiao FC, Lin M, Tai A, Chen G, Huber BT (2006) Cutting edge: Epstein-Barr virus transactivates the HERV-K18 superantigen by docking to the human complement receptor 2 (CD21) on primary B cells. J Immunol 177:2056–2060

Hsiao FC, Tai AK, Deglon A, Sutkowski N, Longnecker R, Huber BT (2009) EBV LMP-2A employs a novel mechanism to transactivate the HERV-K18 superantigen through its ITAM. Virology 385:261–266

Ikejima T, Dinarello CA, Gill DM, Wolff SM (1984) Induction of human interleukin-1 by a product of Staphylococcus aureus associated with toxic shock syndrome. J Clin Invest 73:1312–1320

Junker A, Ivanidze J, Malotka J, Eiglmeier I, Lassmann H, Wekerle H, Meinl E, Hohlfeld R, Dornmair K (2007) Multiple sclerosis: T-cell receptor expression in distinct brain regions. Brain 130:2789–2799

Kaiser R, Obert M, Kaufmann R, Czygan M (1997) IgG-antibodies to CNS proteins in patients with multiple sclerosis. Eur J Med Res 2:169–172

Katoh I, Mírová A, Kurata S, Murakami Y, Horikawa K, Nakakuki N, Sakai T, Hashimoto K, Maruyama A, Yonaga T, Fukunishi N, Moriishi K, Hirai H (2011) Activation of the long terminal repeat of human endogenous retrovirus K by melanoma-specific transcription factor MITF-M. Neoplasia 13:1081–1092

Kewitz S, Staege MS (2013) Expression and regulation of the endogenous retrovirus 3 in Hodgkin's lymphoma cells. Front Oncol 3:179

Kornhuber ME (2006) Nichtentzündliche Pathogenese von Herden bei Multipler Sklerose. Nervenarzt 77:989–990

Kornhuber ME, Ganz C, Lang R, Brill T, Schmahl W (2002) Focal encephalitis in the Lewis rat induced by intracerebral enterotoxin superantigen and amplified by activated intravenous splenocytes. Neurosci Lett 324:93–96

Kornhuber ME, Presek P, Zierz S (2005) Unterschiedliche Wirkung der Immuntherapie auf Schübe und schleichende Progression bei Multipler Sklerose: Deutung und Konsequenzen für die Therapie. Fortschr Neurol Psychiatr 73:143–149

Kremer D, Schichel T, Förster M, Tzekova N, Bernard C, van der Valk P, van Horssen J, Hartung HP, Perron H, Küry P (2013) Human endogenous retrovirus type W envelope protein inhibits oligodendroglial precursor cell differentiation. Ann Neurol 74:721–732

Kwun HJ, Han HJ, Lee WJ, Kim HS, Jang KL (2002) Transactivation of the human endogenous retrovirus K long terminal repeat by herpes simplex virus type 1 immediate early protein 0. Virus Res 86:93–100

La Mantia L, Vacchi L, Di Pietrantonj C, Ebers G, Rovaris M, Fredrikson S, Filippini G (2012) Interferon beta for secondary progressive multiple sclerosis. Cochrane Database Syst Rev 1:CD005181

Lassmann H (2013) Multiple sclerosis: lessons from molecular neuropathology. Exp Neurol. doi:10.1016/j.expneurol.2013.12.003

Lee JR, Ahn K, Kim YJ, Jung YD, Kim HS (2012) Radiation-induced human endogenous retrovirus (HERV)-R env gene expression by epigenetic control. Radiat Res 178:379–384

Levin LI, Munger KL, O'Reilly EJ, Falk KI, Ascherio A (2010) Primary infection with the Epstein-Barr virus and risk of multiple sclerosis. Ann Neurol 67:824–830

Li S, Liu ZC, Yin SJ, Chen YT, Yu HL, Zeng J, Zhang Q, Zhu F (2013) Human endogenous retrovirus W family envelope gene activates the small conductance Ca^{2+}-activated K^{+} channel in human neuroblastoma cells through CREB. Neuroscience 247:164–174

Li F, Nellåker C, Sabunciyan S, Yolken RH, Jones-Brando L, Johansson AS, Owe-Larsson B, Karlsson H (2014) Transcriptional derepression of the ERVWE1 locus following influenza A virus infection. J Virol 88:4328–4337

Liu C, Chen Y, Li S, Yu H, Zeng J, Wang X, Zhu F (2013) Activation of elements in HERV-W family by caffeine and aspirin. Virus Genes 47:219–227

Llorca J, Guerrero-Alonso P, Prieto-Salceda D (2005) Mortality trends of multiple sclerosis in Spain, 1951–1997: an age-period-cohort analysis. Neuroepidemiology 24:129–134

Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H (2000) Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 47:707–717

MacDonald HR, Schneider R, Lees RK, Howe RC, Acha-Orbea H, Festenstein H, Zinkernagel RM, Hengartner H (1988) T-cell receptor V beta use predicts reactivity and tolerance to Mlsa-encoded antigens. Nature 332:40–45

Madigand M, Oger JJ-F, Fauchert R, Sabouraud O, Genetet B (1982) HLA profiles in multiple sclerosis suggest two forms of disease and the existence of protective haplotypes. J Neurol Sci 53:519–529

Mameli G, Astone V, Khalili K, Serra C, Sawaya BE, Dolei A (2007) Regulation of the syncytin-1 promoter in human astrocytes by multiple sclerosis-related cytokines. Virology 362:120–130

Masterman T, Ligers A, Olsson T, Andersson M, Olerup O, Hillert J (2000) HLA-DR15 is associated with lower age at onset in multiple sclerosis. Ann Neurol 48:211–219

Mattson DH, Roos RP, Arnason BG (1980) Isoelectric focusing of IgG eluted from multiple sclerosis and subacute sclerosing panencephalitis brains. Nature 287:335–337

Merabova N, Kaniowska D, Kaminski R, Deshmane SL, White MK, Amini S, Darbinyan A, Khalili K (2008) JC virus agnoprotein inhibits in vitro differentiation of oligodendrocytes and promotes apoptosis. J Virol 82:1558–1569

Nellåker C, Yao Y, Jones-Brando L, Mallet F, Yolken RH, Karlsson H (2006) Transactivation of elements in the human endogenous retrovirus W family by viral infection. Retrovirology 3:44

Nexø BA, Christensen T, Frederiksen J, Møller-Larsen A, Oturai AB, Villesen P, Hansen B, Nissen KK, Laska MJ, Petersen TS, Bonnesen S, Hedemand A, Wu T, Wang X, Zhang X, Brudek T, Maric R, Søndergaard HB, Sellebjerg F, Brusgaard K, Kjeldbjerg AL, Rasmussen HB, Nielsen AL, Nyegaard M, Petersen T, Børglum AD, Pedersen FS (2011) The etiology of multiple sclerosis: genetic evidence for the involvement of the human endogenous retrovirus HERV-Fc1. PLoS One 6:e16652

O'Hare P, Hayward GS (1985) Evidence for a direct role for both the 175,000- and 110,000-molecular-weight immediateearly proteins of herpes simplex virus in the transactivation of delayed-early promoters. J Virol 53:751–760

Olerup O, Hillert J, Fredrikson S, Olsson T, Kam-Hansen S, Möller E, Carlsson B, Wallin J (1989) Primarily chronic progressive and relapsing/remitting multiple sclerosis: two immunogenetically distinct disease entities. Proc Natl Acad Sci USA 86:7113–7117

Ono M, Kawakami M, Ushikubo H (1987) Stimulation of expression of the human endogenous retrovirus genome by female steroid hormones in human breast cancer cell line T47D. J Virol 61:2059–2062

Owens GP, Bennett JL, Lassmann H, O'Connor KC, Ritchie AM, Shearer A, Lam C, Yu X, Birlea M, DuPree C, Williamson RA, Hafler DA, Burgoon MP, Gilden D (2009) Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid. Ann Neurol 65:639–649

Parry A, Corkill R, Blamire AM, Palace J, Narayanan S, Arnold D, Styles P, Matthews PM (2003) Beta-Interferon treatment does not always slow the progression of axonal injury in multiple sclerosis. J Neurol 250:171–178

Parsonnet J, Gillis ZA, Pier GB (1986) Induction of interleukin-1 by strains of Staphylococcus aureus from patients with nonmenstrual toxic shock syndrome. J Infect Dis 154:55–63

Pender MP, Greer JM (2007) Immunology of multiple sclerosis. Curr Allergy Asthma Rep 7:285–292

Perron H, Lang A (2010) The human endogenous retrovirus link between genes and environment in multiple sclerosis and in multifactorial diseases associating neuroinflammation. Clin Rev Allergy Immunol 39:51–61

Perron H, Geny C, Laurent A, Mouriquand C, Pellat J, Perret J, Seigneurin JM (1989) Leptomeningeal cell line from multiple sclerosis with reverse transcriptase activity and viral particles. Res Virol 140:551–561

Perron H, Suh M, Lalande B, Gratacap B, Laurent A, Stoebner P, Seigneurin JM (1993) Herpes simplex virus ICP0 and ICP4 immediate early proteins strongly enhance expression of a retrovirus harboured by a leptomeningeal cell line from a patient with multiple sclerosis. J Gen Virol 74:65–72

Perron H, Garson JA, Bedin F, Beseme F, Paranhos-Baccala G, Komurian-Pradel F, Mallet F, Tuke PW, Voisset C, Blond JL, Lalande B, Seigneurin JM, Mandrand B (1997) Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. The Collaborative Research Group on Multiple Sclerosis. Proc Natl Acad Sci USA 94:7583–7588

Perron H, Jouvin-Marche E, Michel M, Ounanian-Paraz A, Camelo S, Dumon A, Jolivet-Reynaud C, Marcel F, Souillet Y, Borel E, Gebuhrer L, Santoro L, Marcel S, Seigneurin JM, Marche PN, Lafon M (2001) Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. Virology 287:321–332

Perron H, Dougier-Reynaud HL, Lomparski C, Popa I, Firouzi R, Bertrand JB, Marusic S, Portoukalian J, Jouvin-Marche E, Villiers CL, Touraine JL, Marche PN (2013) Human endogenous retrovirus protein activates innate immunity and promotes experimental allergic encephalomyelitis in mice. PLoS One 8:e80128

Pette M, Fujita K, Kitze B, Whitaker JN, Albert E, Kappos L, Wekerle H (1990) Myelin basic protein-specific T lymphocyte lines from MS patients and healthy individuals. Neurology 40:1770–1776

Pickard S, Shankar G, Burnham K (1994) Langerhans' cell depletion by staphylococcal superantigens. Immunology 83:568–572

Prineas JW, Parratt JD (2012) Oligodendrocytes and the early multiple sclerosis lesion. Ann Neurol 72:18–31

Ramagopalan SV, Knight JC, Ebers GC (2009) Multiple sclerosis and the major histocompatibility complex. Curr Opin Neurol 22:219–225

Rott O, Wekerle H, Fleischer B (1992) Protection from experimental allergic encephalomyelitis by application of a bacterial superantigen. Int Immunol 4:347–353

Rott O, Tontsch U, Fleischer B (1993) Dissociation of antigen-presenting capacity of astrocytes for peptide-antigens versus superantigens. J Immunol 150:87–95

Ruebner M, Langbein M, Strissel PL, Henke C, Schmidt D, Goecke TW, Faschingbauer F, Schild RL, Beckmann MW, Strick R (2012) Regulation of the human endogenous retroviral Syncytin-1 and cell-cell fusion by the nuclear hormone receptors PPARγ/RXRα in placentogenesis. J Cell Biochem 113:2383–2396

Ruprecht K, Obojes K, Wengel V, Gronen F, Kim KS, Perron H, Schneider-Schaulies J, Rieckmann P (2006) Regulation of human endogenous retrovirus W protein expression by herpes simplex virus type 1: implications for multiple sclerosis. J Neurovirol 12:65–71

Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, Moutsianas L, Dilthey A, Su Z, Freeman C, Hunt SE, Edkins S, Gray E, Booth DR, Potter SC, Goris A, Band G, Oturai AB, Strange A, Saarela J, Bellenguez C, Fontaine B, Gillman M, Hemmer B, Gwilliam R, Zipp F, Jayakumar A, Martin R, Leslie S, Hawkins S, Giannoulatou E, D'alfonso S, Blackburn H, Martinelli Boneschi F, Liddle J, Harbo HF, Perez ML, Spurkland A, Waller MJ, Mycko MP, Ricketts M, Comabella M, Hammond N, Kockum I, McCann OT, Ban M, Whittaker P, Kemppinen A, Weston P, Hawkins C, Widaa S, Zajicek J, Dronov S, Robertson N, Bumpstead SJ, Barcellos LF, Ravindrarajah R, Abraham R, Alfredsson L, Ardlie K, Aubin C, Baker A, Baker K, Baranzini SE, Bergamaschi L, Bergamaschi R, Bernstein A, Berthele A, Boggild M, Bradfield JP, Brassat D, Broadley SA, Buck D, Butzkueven H, Capra R, Carroll WM, Cavalla P, Celius EG, Cepok S, Chiavacci R, Clerget-Darpoux F, Clysters K, Comi G, Cossburn M, Cournu-Rebeix I, Cox MB, Cozen W, Cree BA, Cross AH, Cusi D, Daly MJ, Davis E, de Bakker PI, Debouverie M, D'hooghe MB, Dixon K, Dobosi R, Dubois B, Ellinghaus D,

Elovaara I, Esposito F, Fontenille C, Foote S, Franke A, Galimberti D, Ghezzi A, Glessner J, Gomez R, Gout O, Graham C, Grant SF, Guerini FR, Hakonarson H, Hall P, Hamsten A, Hartung HP, Heard RN, Heath S, Hobart J, Hoshi M, Infante-Duarte C, Ingram G, Ingram W, Islam T, Jagodic M, Kabesch M, Kermode AG, Kilpatrick TJ, Kim C, Klopp N, Koivisto K, Larsson M, Lathrop M, Lechner-Scott JS, Leone MA, Leppä V, Liljedahl U, Bomfim IL, Lincoln RR, Link J, Liu J, Lorentzen AR, Lupoli S, Macciardi F, Mack T, Marriott M, Martinelli V, Mason D, McCauley JL, Mentch F, Mero IL, Mihalova T, Montalban X, Mottershead J, Myhr KM, Naldi P, Ollier W, Page A, Palotie A, Pelletier J, Piccio L, Pickersgill T, Piehl F, Pobywajlo S, Quach HL, Ramsay PP, Reunanen M, Reynolds R, Rioux JD, Rodegher M, Roesner S, Rubio JP, Rückert IM, Salvetti M, Salvi E, Santaniello A, Schaefer CA, Schreiber S, Schulze C, Scott RJ, Sellebjerg F, Selmaj KW, Sexton D, Shen L, Simms-Acuna B, Skidmore S, Sleiman PM, Smestad C, Sørensen PS, Søndergaard HB, Stankovich J, Strange RC, Sulonen AM, Sundqvist E, Syvänen AC, Taddeo F, Taylor B, Blackwell JM, Tienari P, Bramon E, Tourbah A, Brown MA, Tronczynska E, Casas JP, Tubridy N, Corvin A, Vickery J, Jankowski J, Villoslada P, Markus HS, Wang K, Mathew CG, Wason J, Palmer CN, Wichmann HE, Plomin R, Willoughby E, Rautanen A, Winkelmann J, Wittig M, Trembath RC, Yaouanq J, Viswanathan AC, Zhang H, Wood NW, Zuvich R, Deloukas P, Langford C, Duncanson A, Oksenberg JR, Pericak-Vance MA, Haines JL, Olsson T, Hillert J, Ivinson AJ, De Jager PL, Peltonen L, Stewart GJ, Hafler DA, Hauser SL, McVean G, Donnelly P, Compston A (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476:214–219

Schanab O, Humer J, Gleiss A, Mikula M, Sturlan S, Grunt S, Okamoto I, Muster T, Pehamberger H, Waltenberger A (2011) Expression of human endogenous retrovirus K is stimulated by ultraviolet radiation in melanoma. Pigment Cell Melanoma Res 24:656–665

Schmidt S, Wessels L, Augustin A, Klockgether T (2001) Patients with Multiple Sclerosis and concomitant uveitis/periphlebitis retinae are not distinct from those without intraocular inflammation. J Neurol Sci 187:49–53

Scholl PR, Trede N, Chatila TA, Geha RS (1992) Role of protein tyrosine phosphorylation in monokine induction by the staphylococcal superantigen toxic shock syndrome toxin-1. J Immunol 148:2237–2241

Seo KS, Park JY, Davis WC, Fox LK, McGuire MA, Park YH, Bohach GA (2009) Superantigen-mediated differentiation of bovine monocytes into dendritic cells. J Leukoc Biol 85:606–616

Shirani A, Zhao Y, Karim ME, Evans C, Kingwell E, van der Kop ML, Oger J, Gustafson P, Petkau J, Tremlett H (2012) Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. JAMA 308:247–256

Smith ME, Stone LA, Albert PS, Frank JA, Martin R, Armstrong M, Maloni H, McFarlin DE, McFarland HF (1993) Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. Ann Neurol 33:480–489

Staege MS, Dick T, Reske-Kunz AB (1996) Functionally active T cell receptor/CD3 complexes are present at the surface of cloned cytotoxic T cells without fluorescence-immunological detectability. Cell Immunol 171:62–67

Staege MS, Holtappels R, Thomas D, Reddehase MJ, Reske-Kunz AB (1998) Proliferation and MHC-unrestricted bystander lysis of cytotoxic T cells following antigen self-presentation. Med Microbiol Immunol 187:17–21

Staege MS, Schneider J, Eulitz M, Scholz S, Bornkamm GW, Wölfel T, Reske-Kunz AB (2000) Consequences of antigen self-presentation by tumour-specific cytotoxic T cells. Immunobiology 201:332–346

Staege MS, Gisch K, Reske-Kunz AB (2003) Cytotoxic T cells with reciprocal antigenic peptide presentation function are not generally resistant to mutual lysis. Immunol Cell Biol 81:266–274

Steinman L (2007) Antigen-specific therapy of multiple sclerosis: the long-sought magic bullet. Neurotherapeutics 4:661–665

Stengel S, Fiebig U, Kurth R, Denner J (2010) Regulation of human endogenous retrovirus-K expression in melanomas by CpG methylation. Genes Chromosomes Cancer 49:401–411

Sutkowski N, Conrad B, Thorley-Lawson DA, Huber BT (2001) Epstein-Barr virus transactivates the human endogenous retrovirus HERV-K18 that encodes a superantigen. Immunity 15:579–589

Sutkowski N, Chen G, Calderon G, Huber BT (2004) Epstein-Barr virus latent membrane protein LMP-2A is sufficient for transactivation of the human endogenous retrovirus HERV-K18 superantigen. J Virol 78:7852–7860

Tai AK, O'Reilly EJ, Alroy KA, Simon KC, Munger KL, Huber BT, Ascherio A (2008) Human endogenous retrovirus-K18 Env as a risk factor in multiple sclerosis. Mult Scler 14:1175–1180

Tai AK, Luka J, Ablashi D, Huber BT (2009) HHV-6A infection induces expression of HERV-K18-encoded superantigen. J Clin Virol 46:47–48

Takahashi M, Shinohara F, Takada H, Rikiishi H (2001) Effects of superantigen and lipopolysaccharide on induction of CD80 through apoptosis of human monocytes. Infect Immun 69:3652–3657

Toufaily C, Landry S, Leib-Mosch C, Rassart E, Barbeau B (2011) Activation of LTRs from different human endogenous retrovirus (HERV) families by the HTLV-1 tax protein and T-cell activators. Viruses 3:2146–2159

Trede NS, Geha RS, Chatila T (1991) Transcriptional activation of IL-1 beta and tumor necrosis factor-alpha genes by MHC class II ligands. J Immunol 146:2310–2315

Turcanova VL, Bundgaard B, Höllsberg P (2009) Human herpesvirus-6B induces expression of the human endogenous retrovirus K18-encoded superantigen. J Clin Virol 46:15–19

Van Lambalgen R, Sanders EACM, D'Amaro J (1986) Sex distribution, age of onset and HLA profiles in two types of multiple sclerosis. J Neurol Sci 76:13–21

Vidlak D, Mariani MM, Aldrich A, Liu S, Kielian T (2011) Roles of Toll-like receptor 2 (TLR2) and superantigens on adaptive immune responses during CNS staphylococcal infection. Brain Behav Immun 25:905–914

Vainchtein ID, Vinet J, Brouwer N, Brendecke S, Biagini G, Biber K, Boddeke HW, Eggen BJ (2014) In acute experimental autoimmune encephalomyelitis, infiltrating macrophages are immune activated, whereas microglia remain immune suppressed. In acute experimental autoimmune encephalomyelitis, infiltrating macrophages are immune activated, whereas microglia remain immune suppressed. Glia. doi:10.1002/glia.22711

Yoon S, Bae KL, Shin JY, Yoo HJ, Lee HW, Baek SY, Kim BS, Kim JB, Lee HD (2001) Analysis of the in vivo dendritic cell response to the bacterial superantigen staphylococcal enterotoxin B in the mouse spleen. Histol Histopathol 16:1149–1159

Yu C, Shen K, Lin M, Chen P, Lin C, Chang GD, Chen H (2002) GCMa regulates the syncytin-mediated trophoblastic fusion. J Biol Chem 277:50062–50068