Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Drug Discovery Today: Disease Models
Vol. 32, 2020
Editors-in-Chief
Jan Tornell – AstraZeneca, Sweden
Andrew McCulloch – University of California, SanDiego, USA
Neurovirology

Viral infections and multiple sclerosis

Donatella Donati

Neurologia e Neurofisiologia Clinica, Azienda Ospedaliera Universitaria Senese I 53100 Siena, Italy

The etiology and pathogenesis of MS is likely to involve multiple factors interacting with each other, and the role of infectious and viral agents is still under debate, however a consistent amount of studies suggests that some viruses are associated with the disease. The strongest documentation has come from the detection of viral nucleic acid or antigen or of an anti-viral antibody response in MS patients. A further step for the study of the mechanism viruses might be involved in can be made using *in vitro* and *in vivo* models. While *in vitro* models, based on glial and neural cell lines from various sources are widely used, *in vivo* animal models present challenges. Indeed neurotropic animal viruses are currently used to study demyelination in well-established models, but animal models of demyelination by human virus infection have only recently been developed, using animal gammaherpesviruses closely related to Epstein Barr virus (EBV), or using marmosets expressing the specific viral receptor for Human Herpesvirus 6 (HHV-6). The present review will illustrate the main potential mechanisms of MS pathogenesis possibly associated with viral infections and viruses currently used to study demyelination in animal models. Then the viruses most strongly linked with MS will be discussed, in the perspective that more than one virus might have a role, with varying degrees of interaction, contributing to MS heterogeneity.

E-mail address: (donatid@unisi.it)

Section editor: Donatella Moschettini – Department of Medical Biotechnology, University of Siena, Hospital ``Santa Maria alle Scotte'', Unit Microbiology and Virology, 53100 Siena, Italy.
Donatella Donati – DAI Scienze Neurologiche e Neurosensoriali, Azienda Ospedaliera Universitaria Senese, Siena, Italy.
Steve Jacobson – Chief, Viral Immunology Section, National Institutes of Neurological Disorders and Stroke, National Institutes of Health Bethesda, MD USA.

Multiple sclerosis (MS) is a complex demyelinating disease of the Central Nervous System [1]. Some aspects of its etiology and pathogenesis are still unclear, however it is generally accepted that MS is an inflammatory disease with autoimmune characteristics influenced by environmental or infectious factors in genetically susceptible individuals. These factors are supposed to interplay to varying extent, contributing to the heterogeneity of MS [2].

Mechanisms of MS pathogenesis possibly associated with viral infections

The typical MS lesions are multiple perivascular white matter plaques of demyelination associated with various degrees of inflammatory cells [3,4]. Additionally diffuse neurodegeneration and plaque-like demyelination has also been described in the deep and cortical grey matter [5–8].

The possible involvement of viral agents has been suggested by the detection of viral nucleic acid, protein or antiviral antibodies in the blood, CSF or brain tissue, and several viruses have been specifically associated with MS, though a definitive cause-effect relationship has not been demonstrated. Virus infections might contribute to MS through different mechanisms in various combinations [9,10]. These are direct toxicity, molecular mimicry, dual T

1740-6757/$ © 2020 Published by Elsevier Ltd. https://doi.org/10.1016/j.ddmod.2020.02.003

cell receptor, bystander activation and epitope spreading, briefly outlined below.

Direct toxicity

Though clinical and experimental evidence accounts for an autoimmune pathogenetic mechanism for MS development, the presence of a direct viral toxic mechanism on actively infected neural cells cannot be ruled out, on the basis of detection of cellular damage not related to inflammation or autoimmunity. Indeed oligodendrocytic dystrophy without IgG and complement deposition, as if a direct damage would occur, has been found in some MS plaques [3], and primary defective oligodendrocyte precursor cells contributing to blood-brain barrier (BBB) dysfunction and disease perpetuation have recently been demonstrated [11].

Molecular mimicry

Molecular mimicry is the mechanism by which an immune cross-reaction towards myelin components can be induced by homologous viral sequences [12] or structurally similar peptides [13] through presentation by major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APCs) to autoreactive CD4 + T cells. A number of viruses have been demonstrated to induce disease at least in part through this mechanism, as in the case of HSV-induced stromal cheratitis [14] and Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease (TMEV-IDD) [15].

Dual T cell receptor (TCR)

The possibility that a T cell can carry more than one TCR, contrasting with previous assumption, has been demonstrated [16], suggesting that some T cells might carry two different combinations of TCR, specific for both myelin and viral antigens respectively and upon activation would react against both antigens [17].

Bystander activation

Bystander activation implies that a viral infection can elicit an over-reactive inflammatory response due to tissue damage and consequent unveiling and presentation by APCs of hidden autoantigens and production of novel autoreactive T cells and plasma cells [18].

Epitope spreading

The mechanisms illustrated above, damaging myelin-producing cells, would cause release of myelin fragments in the inflammatory environment, triggering a self-sustained breakdown of myelin, with additional recognition of further epitopes [17]. This process, known as epitope spreading, was first described by Lehman et al. [19] and has been studied in TMEV-IDD [15].

Models of demyelination

Several models of demyelination are known [20,21]. *In vitro* models based on glial cell lines include the use of oligodendrocyte [22,23], astrocyte [24,25] and microglial [26,27] cell lines [28] and progenitor-derived glial cells [29–33]. *In vivo* models include the most extensively studied animal model for MS, experimental autoimmune encephalomyelitis (EAE), obtained by immunization with myelin proteins with adjuvants, or passive transfer of autoreactive T cells with or without pathogenic auto-antibodies in susceptible animals [34–37].Various clinical types of EAE can be induced in rodents and primates (marmosets and rhesus macaques), ranging from acute monophasic [38] to a chronic course, either relapsing/remitting [39] or chronic progressing [40]. EAE can also develop after induction of toxic agents, such as cuprizone [41], lysophosphatidilcholine [42], ethidium bromide [43]. EAE can also occur spontaneously in transgenic mice expressing a T-cell receptor specific for myelin oligodendrocyte glycoprotein (MOG) [44].

Viral models of demyelination

Semliki forest virus (SFV)

The strains of alphavirus SFV commonly used are the mutant variant M9, highly virulent, and the avirulent A7 strain. This latter strain has been more widely studied and can cause an acute secondary demyelination with encephalomyelitis after viral clearance in B6 and, in a milder form, SJL mice [45]. During the demyelinating phase the virus is not found in the CNS and a molecular mimicry between viral surface glycoprotein E2 and MOG peptide 8–32 has been demonstrated, with production of cross-reactive T cells and antibodies [46]. Additionally, SFV induces the expression of adhesion molecules, among which VLA-4 [47], in the CNS.

Mouse hepatitis virus (MHV)

The coronavirus MHV can infect humans, mice, rats and non-human primates [48]. After intracranial inoculation of susceptible mice, MHV induces an acute severe encephalomyelitis infecting oligodendrocytes, astrocytes and microglia. After two weeks of infection the viral loads in the surviving animals are undetectable, but oligodendroglial expression of viral antigen is detected, accounting for viral persistence, with the development of a chronic immune-mediated demyelinating disease [49]. Infiltrating T cells and macrophages are thought to be the main effectors of demyelination, with a possible additional role for a direct toxic effect due to viral persistence in oligodendrocytes. Interestingly, in chronic demyelinating lesions endogenous remyelination has been documented [50]. Since remyelination can occur also in MS [51], MHV can be considered as a valid model to study specific aspects of MS pathogenesis.

TMEV

The demyelinating disease induced by TMEV, a natural enteric pathogen of mice, can be considered the most relevant virus-induced animal model of MS. TMEV-IDD has interesting similarities with MS, since the virus establishes a persistent infection resembling the chronically progressive form of MS, with myelin reactive T cells and anti-myelin antibodies. Furthermore, mice with TMEV-IDD can undergo spontaneous remyelination with partial recovery of neurological functions, as observed in MS [52]. These features refer to the TO TMEV subgroup, including the DA and BeAn strains. The other viral subgroup, namely GDVII, includes the strains GDVII and FA and is extremely virulent, causing death within 2 weeks after infection. Infection of SJL/J mice is characterized by an acute phase, between day 3 and 10, in which viral antigens and genome are found in neurons [53], followed by a decrease of the viral load, with incomplete clearance. A chronic phase then ensues 1 month after inoculation, with viral persistence in oligodendrocytes, astrocytes and microglia/macrophages [54]. The subsequent immune reaction does not eliminate the virus, but leads to a chronic inflammation, driven by virus-specific CD4 + T cell response, self-sustained by epitope spreading [15], with immune response against myelin proteins [55].

Japanese macaque encephalomyelitis rhadinovirus (JMERV)

Japanese macaque encephalomyelitis (JME), a spontaneous inflammatory demyelinating disease similar to MS, was first reported in 2011 in a colony of Japanese macaques and associated to a novel simian herpesvirus, JMERV [56]. Viral genomic characterization revealed that JMERV is a gamma-2 herpesvirus closely related to rhesus macaque rhadinovirus and human herpesvirus 8 [57]. Immunopathological analysis documented the presence of several key signatures associated with MS, such as CNS-infiltrating T cells with Th1 and Th17 phenotypes besides MRI similarities, suggesting a potential use as an MS model [58].

Human viruses and multiple sclerosis

Though no MS-specific virus has been found so far, investigation in this area has continued based on epidemiological and laboratory data [9,59]. Due to the complexity and heterogeneity of MS it is possible that more than one viral agent is involved [60]. Additionally, as well as commensal bacteria, ubiquitous viruses composing a common flora of viruses, named virome, might challenge and shape the immune system similarly and/or complementarily to bacterial common flora [61,62].

Epstein–Barr virus (EBV)

The prevalence of EBV seropositivity in the world's population is approximately 95% [63], while almost 100% of MS patients are seropositive [64]. Moreover, a history of infectious mononucleosis significantly increases the risk of MS [65] and CSF-restricted EBV-specific oligoclonal bands (OCB) in a subset of MS patients has been detected [66,67] though the specificity of such result is still under debate [68]. Contrary to the unequivocal serological data, the search of EBV in MS brain has generated conflicting results, which were studied by the NeuroproMiSe EBV Working Group with the final conclusion that an unequivocal proof of EBV CNS infection in MS is lacking [69]. On this basis it has been hypothesized that EBV would rescue ''forbidden'' memory B cells directed against a CNS epitope [70]. To explain the inconsistent detection of EBV in MS lesions, it has been suggested that EBV memory B cells would lose the episomic EBV DNA upon replication, but would retain the ''forbidden'' epitope recognition, possibly activating a molecular mimicry mechanism [71]. Additionally, a ''two hit hypothesis'' has been formulated to explain the association of EBV infection with MS: during primary infection EBV would disrupt BBB permeability, allowing activated immune cells to enter the CNS thus generating a cascade of events leading to CNS inflammation [72,73].

Animal models for EBV infections use mice infected with murine gammaherpesvirus 68, a mouse pathogen, which upon induction show an accelerated course of EAE [74], or marmosets naturally infected with the gamma1-herpesvirus callitrichine herpesvirus 3 (CalHV3) which, similarly to EBV, infects and immortalizes B cells [75]. It has been demonstrated that CalHV3-infected B cells can act as antigen presenting cells (APCs) not only *via* MHC class II molecules to CD4 T cells, but also *via* MHC class I molecules to CD8 T cells [76]. Using this model, a conversion from a tolerogenic destructive processing of MOG peptide to productive processing and autoaggressive T cell activation was demonstrated [77].

Very interesting results come from a recent study showing that MS patient sera, differently from healthy controls, recognize unique EB nuclear antigen (EBNA) 411–426 epitopes with antibodies cross-reacting with myelin basic protein (MBP). Moreover SJL/J and Balb/c mice injected with EBNA 411-426 peptide develop signs of EAE [78]. Based on these findings, a new line of investigation can be developed for a further insight into the possible role of EBV through molecular mimicry in MS pathogenesis.

Human herpesvirus 6 (HHV-6)

An association of HHV-6 with MS has been suggested since 1993 [79] and has focused a wide number of studies [80]. Two HHV-6 species are known, HHV-6 A and HHV-6 B, sharing a 95% homology [81]. HHB-6 B accounts for most symptomatic infections during infancy, including exanthema subitum (or roseola infantum), after which it can establish latency. The prevalence of HHV-6A (currently not associated with a distinctive disease) is not known due to the cross-reactivity of HHV-6A and HHV-6 B antibodies, however early studies documented an HHV -6A higher detection rate in the CSF than in PBMCs [82]. Viral DNA persists in episomes but can

also integrate into host cell chromosomes, with a prevalence of approximately 0.85% in the general population [83], and neural cells can be a site of latency.

A considerable number of studies, summarized by Virtanen and Jacobson [9], have demonstrated an association between HHV-6 and MS, either by direct DNA detection in MS lesions or increased antiviral antibody titres in MS patients though other investigators did not confirm this association [84]. Interestingly, a sequence homology between HHV-6 protein U24 and myelin basic protein [85] and cross-reactivity of autoreactive T-cells with MBP [86] has been demonstrated, suggesting a molecular mimicry mechanism.

For cellular entry HHV-6 uses the complement regulatory receptor CD46 [87], which is expressed in adult oligodendrocytes, astrocytes and microglial cells [88], accounting for viral neurotropism. While CD46 is missing in rodents, it is expressed in the common marmoset (*Callithrix jacchus*), which can be used as a model not only for MS by EAE induction [89], but also for the study of HHV-6 infection [90]. Very promising results were obtained in EAE marmosets previously infected intranasally with HHV-6, which showed a significant accelerated EAE compared to uninfected animals [91]. Moreover HHV-6 antigen expression was upregulated in EAE lesions, similarly to what observed in MS [92,93] and a decrease of naïve CD8 cells with a peripheral expansion of effector/memory CD8+ cells correlating with EAE duration in HHV-6/EAE marmoset was documented. In the light of these findings, the authors concluded that HHV-6 might prime the immune system, creating a ''fertile field'' for the expansion of autoaggressive T cells, then triggered by other environmental factors [94].

Human endogenous retroviruses (HERVs)

HERVs were incorporated in the human genome millions of years ago and the presence and/or activation of three HERVs (HERV H, HERV K and HERV W), has been associated with MS [95,96].

The findings would suggest that HERV activation might trigger a demyelination process, contributing to MS progression [97]. HERVs can be activated by several simuli, including viruses such as VZV, HSV-1, EBV and HHV-6 [98], however the most widely studied association is with EBV. Indeed the HERV W MS-associated retrovirus (MSRV) activation during infectious mononucleosis and the notion of the high prevalence of EBV positivity in MS would suggest that MSRV activation might possibly act as an effector in MS, being triggered by EBV latent infection [99]. Again this viral interaction would be in agreement with the theory of a ''fertile field'' [94], created in this case by a previous EBV infection.

It has been demonstrated that injection of a MOG peptide in an emulsion containing MRSV Env protein instead of complete Freund adjuvant can induce EAE in mice, providing a model to study the role of MSRV in MS [100].

Measles, Rubella and Varicella Zoster (VZ) viruses

It has been demonstrated that the intrathecal polyspecific humoral response of MS patients has Measles, Rubella and VZ viruses (MRV) as its most frequent component [101], providing a useful help for MS diagnosis. Moreover VZV infection is associated with higher risk of developing MS [102]. However appropriate animal models for the study of a role in MS are lacking, despite some attempts for the study of VZV neurotropism [103].

Conclusions

In conclusion, the role of viral infections in MS has still to be defined, and the possibility that more than one virus is involved in MS pathogenesis should be taken into account. Moreover the possible degrees of interaction between viruses and other infections or environmental and genetic factors might vary to a great extent, consistently with MS heterogeneity. The detection of viral components in MS lesions or anti-viral immune response in MS patients associated with clinical relapses are highly suggestive of a role for viruses, possibly either as triggers or co-factors in the development of the disease. However the ubiquity and the specificity for humans of these viruses make it difficult to study possible mechanisms. For this reason the establishment of new models of MS in infected animals is very promising, and provides an important tool to shed light into the definition of viral role in MS.

Conflict of interest

I have no conflict of interest.

References

[1] Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Eng J Med 2018;378(2):169–80.
[2] Tarlinton RE, Khaibullin T, Granatov E, Martynova E, Rizvanov A, Khaiboullina S. The interaction between viral and environmental risk factors in the pathogenesis of multiple sclerosis. Int J Mol Sci 2019;20: E303.
[3] Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000;47(6):707–17.
[4] Lassman H. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. Front Immunol 2019;9:3116.
[5] Haider L, Simeonidou C, Steinberger G, Hametner S, Grigoriadis N, Deretzi G, et al. Multiple sclerosis deep gray matter: the relation between demyelination, neurodegeneration, inflammation and iron. J Neurol Neurosurg Psychiatry 2014;85:1386–95.
[6] Calabrese M, Magliozzi R, Ciccarelli O, Geurts JJ, Reynolds R, Martin R. Exploring the origins of grey matter damage in multiple sclerosis. Nat Rev Neurosci 2015;16:147–58.
[7] Calabrese M, Castellaro M. Cortical gray matter MR imaging in multiple sclerosis. Neuroimaging Clin N Am 2017;27:301–12.
[8] Fischer MT, Wimmer I, Höftberger R, Gerlach S, Haider L, Zrzavy T, et al. Disease-specific molecular events in cortical multiple sclerosis lesions. Brain 2013;136:1799–815. http://dx.doi.org/10.1093/brain/awt110.
[9] Virtanen JO, Jacobson S. Viruses and multiple sclerosis. CNS Neurol Disord Drug Targets 2012;11:528–44.
[10] Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence. Infections and

autoimmune disease. Clin Microbiolo Rev 2006;19:80–94. http://dx.doi.org/10.1128/CMR.19.1.80-94.2006.
[11] Niu J, Tsai HH, Hoi KK, Huang N, Yu G, Kim K, et al. Aberrant oligodendroglial-vascular interactions disrupt the blood-brain barrier, triggering CNS inflammation. Nat Neurosci 2019;22:709–18. http://dx.doi.org/10.1038/s41593-019-0369-4.
[12] Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 1985;230:1043–5.
[13] Wucherpfennig KW, Strominger JL. Molecular mimicry in T-cell mediated autoimmunity: viral peptides activate human T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 1995;80:695–705.
[14] Zhao Z, Granucci F, Yeh L, Schaffer PA, Cantor H. Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection. Science 1998;279:1344–7.
[15] Croxford J, Olson JK, Miller SD. Epitope spreading and molecular mimicry as triggers of autoimmunity in the Theiler's virus-induced demyelinating disease model of multiple sclerosis. Autoimmun Rev 2002;1:251–60.
[16] Gavin MA, Rudensky AY. Dual TCR T cells: gaining entry into the periphery. Nat Immunol 2002;3:109–10.
[17] Cusick MF, Libbey JE, Fujinami RS. Multiple sclerosis: autoimmunity and viruses. Curr Opin Rheumatol 2013;25(4). 496-50.
[18] Duke RC. Self recognition by T cells. I. Bystander killing of target cells bearing syngeneic MHC antigens. J Exp Med 1995;170:59–71.
[19] Lehman PV, Forsthuber T, Miller A, Sercarz EE. Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. Nature 1992;358:155–7.
[20] Osorio-Querejeta I, Sáenz-Cuesta M, Muñoz-Culla M, Otaegui D. Models for studying myelination, demyelination and remyelination. Neuromol Med 2017;19:181–92.
[21] van der Star BJ, Vogel DY, Kipp M, Puentes F, Baker D, Amor S. In vitro and in vivo models of multiple sclerosis. CNS Neurol Disord Drug Targets 2012;11:570–88.
[22] Richter-Landsberg C, Heinrich M. OLN-93: a new permanent oligodendroglia cell line derived from primary rat brain glial cultures. J Neurosci Res 1996;45:161–73.
[23] Buntinx M, Vanderlocht J, Hellings N, Vandenabeele F, Lambrichts I, Raus J, et al. Characterization of three human oligodendroglial cell lines as a model to study oligodendrocyte injury: morphology and oligodendrocyte-specific gene expression. J Neurocytol 2003;31:25–38.
[24] Amara FM, Junaid A, Clough RR, Liang B. TGF-β1, regulation of Alzheimer amyloid precursor protein mRNA expression in a normal human astrocyte cell line: mRNA stabilization. Mol Brain Res 1999;71:42–9.
[25] Price TN, Burke JF, Mayne LV. A novel human astrocyte cell line [A735] with astrocytic-specific neurotransmitter function. In Vitro Cell Dev Biol Anim 1999;35:279–88.
[26] Walker WS, Gatewood J, Olivas E, Askew D, Havenith CE. Mouse microglial cell lines differing in constitutive and interferon-gamma-inducible antigen-presenting activities for naive and memory CD4+ and CD8+ T cells. J Neuroimmunol 1995;63:163–74.
[27] Janabi N, Peudenier S, Héron B, Na KH, Tardieu M. Establishment of human microglial cell lines after transfection of primary cultures od embryonic microglial cells with the SV40 large T antigen. Neurosci Lett 1995;195:105–8.
[28] De Vries G. Glial cell lines: an overview. Neurochemical Res 2010;35:1978–2000.
[29] Kurtzberg J. Isolation and expansion of oligodendrocyte progenitor cells from cryopreserved human umbilical cord blood. Isolation 2011;13:722–9. http://dx.doi.org/10.3109/14653249.2011.553592.
[30] Ogawa S, Tokumoto Y, Miyake J, Nagamune T. Immunopanning selection of A2B5-positive cells increased the differentiation efficiency of induced pluripotent stem cells into oligodendrocytes. Neurosci Lett 2011;489:79–83. http://dx.doi.org/10.1016/j.neulet.2010.11.070.
[31] Medina-Rodríguez EM, Arenzana FJ, Bribián A, de Castro F. Protocol to isolate a large amount of functional oligodendrocyte precursor cells from the cerebral cortex of adult mice and humans. PLoS One 2013;26(8) e81620. http://dx.doi.org/10.1371/journal.pone.0081620.
[32] Tcw J, Wang M, Pimenova AA, Bowles KR, Hartley BJ, Lacin E, et al. An efficient platform for astrocyte differentiation from human induced pluripotent stem cells. Stem Cell Rep 2017;9:600–14. http://dx.doi.org/10.1016/j.stemcr.2017.06.018.
[33] Donati D, Martinelli E, Cassiani-Ingoni R, Ahlqvist J, Hou J, Major EO, et al. Variant-specific tropism of human herpes virus 6 in human astrocytes. J Virol 2005;79:9434–48. http://dx.doi.org/10.1128/JVI.79.15.9439–9448.2005.
[34] Wolf A, Kabat EA, Bezer AE. The pathology of acute disseminated encephalomyelitis produced experimentally in the rhesus monkey and its resemblance to human demyelinating disease. J Neuropathol Exp Neurol 1947;6:333–57.
[35] Ben-Nun A, Wekerle H, Cohen IR. The rapid isolation of clonable antigen-specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis. Eur J Immunol 1981;11:195–9. http://dx.doi.org/10.1002/eji.1830110307.
[36] Lassmann H, Bradl M. Multiple sclerosis: experimental models and reality. Acta Neuropathol 2017;133:223–44. http://dx.doi.org/10.1007/s00401-016-1631-4.
[37] Steinman L. Myelin-specific CD8 T cells in the pathogenesis of experimental allergic encephalitis and multiple sclerosis. J Exp Med 2001;194(5):27–30.
[38] Amor S, O'Neill JK, Morris MM, Smith RM, Wraith DC, Groome N, et al. Encephalitogenic epitopes of myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein for experimental allergic encephalomyelitis induction in Biozzi ABH [H-2Ag7] mice share an amino acid motif. J Immunol 1996;156:3000–8.
[39] Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol 2004;55:458–68. http://dx.doi.org/10.1002/ana.20016.
[40] Hampton DW, Serio A, Pryce G, Al-Izki S, Franklin JM, Giovannoni G, et al. Neurodegeneration progresses despite complete elimination of clinical relapses in a mouse model of multiple sclerosis. Acta Neuropath Commun 2013;1:84. http://dx.doi.org/10.1186/2051-5960-1-84.
[41] Praet J, Guglielmetti C, Berneman Z, Van der Linden A, Ponsaerts P. Cellular and molecular neuropathology of the cuprizone mouse model: clinical relevance for multiple sclerosis. Neurosci Behav Rev 2014;47:485–505. http://dx.doi.org/10.1016/j.neubiorev.2014.10.004.
[42] Jeffery ND, Blakemoore WF. Remyelination of mouse spinal cord axons demyelinated by local injection of lysolecithin. J Neurocytol 1995;24:775–81. http://dx.doi.org/10.1007/BF01191213.
[43] Blakemore WF. Ethidium bromide induced demyelination in the spinal cord of the cat. Neuropath Appl Neurobiol 1982;8:365–75. http://dx.doi.org/10.1111/j.1365-2990.1982.tb00305.x.
[44] Pöllinger B, Krishnamoorthy G, Berer K, Lassmann H, Bösl MR, Dunn R, et al. Spontaneous relapsing-remitting EAE in the SJL/J mouse: MOG reactive transgenic T cells recruit endogenous MOG-specific B cells. J Exp Med 2009;206:1303–16. http://dx.doi.org/10.1084/jem.20090299.
[45] Mokhtarian F, Wesselingh SL, Choi S, Maeda A, Griffin DE, Sobel RA, et al. Production and role of cytokines in the CNS of mice with acute viral encephalomyelitis. J Neuroimmunol 1996;66:11–22.
[46] Mokhtarian F, Zhang Z, Shi Y, Gonzales E, Sobel RA. Molecular mimicry between a viral peptide and a myelin oligodendrocyte glycoprotein peptide induces autoimmune demyelinating disease in mice. J Neuroimmunol 1999;95:43–54.
[47] Smith JP, Morris-Downes M, Brennan FR, Wallace GJ, Amor S. A role for α4-integrin in the pathology following Semliki Forest virus infection. J Immunol 2000;106:60–8.
[48] Stohlman SA, Hinton DR. Viral induced demyelination. Brain Pathol 2000;11:92–106.
[49] Hosking MP, Lane TE. The pathogenesis of murine coronavirus infection of the central nervous system. Crit Rev Immunol 2010;30:119–30.
[50] Hatch MN, Schaumburg CS, Lane TE, Keirstead HS. Endogenous remyelination is induced by transplant rejection in a viral model of multiple sclerosis. J Neuroimmunol 2009;212:74–81.

[51] Brück W, Kuhlmann T, Stadelmann C. Remyelination in multiple sclerosis. J Neurol Sci 2003;206:181–5.
[52] DePaula-Silva AB, Hanak TJ, Libbey JE, Fujinami RS. Theiler's murine encephalomyelitis infection of SJL/J and C57BL/6J mice: models for multiple sclerosis and epilepsy. J Neuroimmunol 2017;308:30–42.
[53] Tsunoda I, Kurtz CI, Fujinami RS. Apoptosis in acute and chronic central nervous system induced by Theiler's murine encephalomyelitis virus. Virology 1997;228:388–93.
[54] Oleszak EL, Chang JR, Friedman H, Katsetos CD, Platsoucas CD. Theiler's virus infection: a model for multiple sclerosis. Clin Microbiol Rev 2004;17:174–207.
[55] Katz-Levy Y, Neville KL, Padilla J, Rahbe S, Begolka WS, Girvin AM, et al. Temporal development of autoreactive Th1 responses and endogenous presentation of self myelin epitopes by central nervous system-resident APCs in Theiler's virus-infected mice. J Immunol 2000;165:5304–14.
[56] Axthelm MK, Bourdette DN, Marracci GH, Su W, Mullaney ET, Manoharan S, et al. Japanese macaque encephalomyelitis: a spontaneous multiple sclerosis-like disease in a nonhuman primate. Ann Neurol 2011;70:362–73.
[57] Estep RD, Hansen SG, Rogers KS, Axthelm MK, Wong SW. Genomic characterization of Japanese macaque rhadinovirus, a novel herpesvirus isolated from a nonhuman primate with a spontaneous inflammatory demyelinating disease. J Virol 2013;87:512–23.
[58] Blair TC, Manoharan M, Rawlings-Rhea SD, Tagge I, Kohama SG, Woltjer RL, et al. Immunopathology of Japanese macaque encephalomyelitis is similar to multiple sclerosis. J Neuroimmunol 2016;291:1–10.
[59] Smatti MK, Cyprian FS, Nasrallah GK, Al Tani AA, Almishal RO, Yassine HM. Viruses and autoimmunity: a review on the potential interaction and molecular mechanisms. Viruses 2019;11:762. http://dx.doi.org/10.3390/v11080762.
[60] Steiner I, Sriram S. The ''one virus, one disease'' model of multiple sclerosis is too constraining. Ann Neurol 2007;62(529). author reply 529.
[61] Virgin HW, Wherry EJ, Ahmed R. Redifining chronic viral infection. Cell 2009;138:30–50.
[62] Foxman EF, Iwasaki A. Genome-virome interactions: examining the role of common viral infections in complex disease. Nat Rev Microbiol 2011;9:254–64.
[63] Luzuriaga K, Sullivan JL. Infectious mononucleosis. New Engl J Med 2000;362:1993–2000.
[64] Pakpoor J, Disanto G, Gerber JE, Dobson R, Meier UC, Giovannoni G, et al. The risk of developing multiple sclerosis in individuals seronegative for Epstein-Barr virus: a meta analysis. Mult Scler J 2013;19:162–6.
[65] Handel AE, Williamson AJ, Disanto G, Handunnetthi L, Giovannoni G, Ramagopalan SV. An updated meta-analysis of risk of multiple sclerosis following infectious mononucleosis. PLoS One 2010;5e12496.
[66] Rand KH, Houck H, Denslow ND, Heilman KM. Epstein-Barr virus nuclear antigen-1 [EBNA-1] associated oligoclonal bands in patients with multiple sclerosis. J Neuroimmunol 2000;173:32–9.
[67] Virtanen JO, Wohler J, Fenton K, Reich DS, Jacobson S. Oligoclonal bands in multiple sclerosis reactive against two herpesviruses and association with magnetic resonance imaging findings. Mult Scler 2014;20:27–34.
[68] Castellazzi M, Contini C, Tamborino C, Fasolo F, Roversi G, Seraceni S, et al. Epstein-Barr virus-specific intrathecal oligoclonal IgG production in relapsing-remitting multiple sclerosis is limited to a subset of patients and is composed of low affinity antibodies. J Neuroinflammation 2014;11:188. http://dx.doi.org/10.1186/s12974-014-0188-1.
[69] Lassmann H, Niedobitek G, Aloisi F, Middldorp JM, NeuroproMiSe EBV Working Group. Epstein-Barr virus in the multiple sclerosis brain: a controversial issue—report on a focused workshop held in the centre for brain research of the medical university of Vienna, Austria. Brain 2011;134:2772–86.
[70] Pender MP. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. Trends Immunol 2003;24:584–8.
[71] Laurence M, Benito-Léon J. Epstein-Barr virus and multiple sclerosis: updating Pender's hypothesis. Mult Scler Relat Disord 2017;16:8–14.
[72] Ransohoff RM, Engelhardt B. The anatomical and cellular basis of immune surveillance in the central nervous system. Nat Rev Immunol 2012;12:623–35.
[73] Guan Y, Jakimovski D, Ramanathan M, Weinstock-Guttman B, Zivadinov R. The role of Epstein-Barr virus in multiple sclerosis: from molecular pathophysiology to in vivo imaging. Neural Regen Res 2019;14:373–86.
[74] Casiraghi C, Shanina I, Cho S, Freeman M, Blackman MA. Gammaherpesvirus latency accentuates EAE pathogenesis: relevance to Epstein-Barr virus and multiple sclerosis. PLoS Pathog 2012;8(5) e1002715.
[75] Ehlers B, Spiess K, Leendertz F, Peeters M, Boesch C, Gatherer D, et al. Lymphocryptovirus phylogeny and the origins of Epstein-Barr virus. J Gen Virol 2010;91:630–42.
[76] Jagessar SA, Holtman IR, Hofman S, Morandi E, Hejimans N, Laman JD, et al. Lymphocryptovirus infection of nonhuman primate B cells converts destructive into productive processing of the pathogenic CD8 T cell epitope in myelin oligodendrocyte glycoprotein. J Immunol 2016;197:1074–88.
[77] 't Hart BA, Kap Y. An essential role of virus-infected B cells in the marmoset experimental autoimmune encephalomyelitis model. Mult Scler J Exp Transl Clin 2017;3(1)2055217317690184. http://dx.doi.org/10.1177/2055217317690184.
[78] Jog NR, McClain MT, Heinlen LD, Gross T, Towner R, Guthridge JM, et al. Epstein Barr virus nuclear antigen 1 [EBNA-1] peptides recognized by adult multiple sclerosis patient sera induce neurologic symptoms in a murine model. J Autoimmun 2019;9102332.
[79] Sola P, Merelli E, Marasca R, Poggi M, Luppi M, Montorsi M, et al. Human herpes virus 6 and multiple sclerosis: survey of anti-HHV-6 antibodies by immunofluorescence analysis and of viral sequence by polymerase chain reaction. J Neurol Neurosurg Psychiatry 1993;56:917–9.
[80] Leibovitch EC, Jacobson S. Viruses in chronic progressive neurologic disease. Mult Scler 2018;24(48):52.
[81] Ablashi D, Agut H, Alvarez-Lafuente A, Clark DA, Dewhurst S, DiLuca D, et al. Classification of HHV-6A and HHV-6B as distinct viruses. Arch Virol 2014;159:863–70.
[82] Hall CB, Caserta MT, Schnabel KC, Long C, Epstein LG, Insel RA, et al. Persistence of human herpesvirus 6 according to site and variant: possible greater neurotropism of variant A. Clin Infect Dis 1998;26:132–7.
[83] Pellett P, Ablashi DV, Ambros PF, Agut H, Caserta MT, Descamps V, et al. Chromosomally integrated human herpesvirus 6: questions and answers. Rev Med Virol 2012;22:144–55.
[84] Merelli E, Bedin R, Sola P, Barozzi P, Mancardi GL, Ficarra G, et al. Human herpes virus 6 and human herpes virus 8 DNA sequences in brains of multiple sclerosis patients, normal adults and children. J Neurol 1997;244:450–4.
[85] Tejada-Simon MV, Zang YC, Hong J, Rivera VM, Zhang JZ. Cross-reactivity with myelin basic protein and human herpesvirus-6 in multiple sclerosis. Ann Neurol 2003;53:189–97.
[86] Cheng W, Ma Y, Gong F, Hu C, Qian L, Huang Q, et al. Cross-reactivity of autoreactive T cells with MBP and viral antigens in patients with MS. Front Biosci [Landmark Ed] 2012;17:1648–58.
[87] Santoro F, Kennedy PE, Locatelli G, Malnati MS, Berger EA, Lusso P. CD46 is a cellular receptor for human herpesvirus 6. Cell 1999;99:817–27.
[88] Cassiani-Ingoni R, Greenstone HL, Donati D, Gogdell-Hahn A, Martinelli E, Refai D, et al. CD46 on glial cells can function as a receptor for viral glycoprotein-mediated cell-cell fusion. Glia 2005;52:252–8.
[89] 't Hart BA, Massacesi L. Clinical, pathological, and immunological aspects of the multiple sclerosis model in common marmosets (*Callithrix jacchus*). J Neuropathol Exp Neurol 2009;68:341–55.
[90] Leibovitch E, Wohler JE, Macri CSM, Motanic K, Harberts E, Gaitán MI, et al. Novel marmoset model of human Herpesvirus 6A and 6B infections: immunologic, virologic and radiologic characterization. PLoS Pathog 2013;9e1003138.
[91] Leibovitch EC, Caruso B, Ha SK, Schindler MK, Lee NJ, Luciano NJ, et al. Herpesvirus trigger accelerates neuroinflammation in a non human primate model of multiple sclerosis. Proc Natl Acad Sci U S A 2018;115:11292–97.
[92] Challoner PB, Smith KT, Parker JD, MacLeod DL, Sn Coulter, Rose TM, et al. Plaque-associated expression of human herpesvirus 6 in multiple sclerosis. Proc Natl Acad Sci U S A 1995;92:7440–4.

[93] Goodman AD, Mock DJ, Powers JM, Baker JV, Blumberg BM. Human herpesvirus 6 genome and antigen in acute multiple sclerosis lesions. J Infect Dis 2003;187:1365–76.
[94] Von Herrrath MG, Fujinami RS, Whitton JL. Microorganisms and autoimmunity: making the barren field fertile? Nat Rev Microbiol 2003;1:151–7.
[95] Küri P, Nath A, Créange A, Dolei A, Marche P, Gold J, et al. Human endogenous retroviruses in neurological diseases. Trends Mol Med 2018;24:379–94.
[96] Morandi E, Tanasescu R, Tarlinton RE, Constantinescu CC, Zhang W, Tench C, et al. The association between human endogenous retroviruses and multiple sclerosis: a systematic review and metanalysis. PLoS One 2017;12:e0172415.
[97] Arneth B. Up-to-date knowledge about the association between multiple sclerosis and the reactivation of human endogenous retrovirus infections. J Neurol 2018;265:1733–9.
[98] Perron H, Bernard C, Bertrand JB, Lang AB, Popa I, Sanhadji K, et al. Endogenous retroviral genes, herpesviruses and gender in multiple sclerosis. J Neurol Sci 2009;286:65–72.
[99] Mameli G, Madeddu G, Mei A, Uleri E, Poddighe L, Delogu LG, et al. Activation of MRSV-type endogenous retroviruses during infectious mononucleosis and Epstein-Barr virus latency: the missing link with multiple sclerosis? PLoS One 2013;8(11)e78474.
[100] Perron H, Dougier-Reynaud H-L, Lomparski C, Popa I, Firouzi R, Bertrand JB, et al. Human endogenous retrovirus protein activates innate immunity and promotes experimental allergic encephalomyelitis in mice. PLoS One 2013;8e80128.
[101] Jarius S, Eichhorn P, Franciotta D, Petereit HF, Akman-Demir G, Wick M, et al. The MRZ reaction as a highly specific marker of multiple sclerosis: re-evaluation and structured review of the literature. J Neurol 2017;264:453–66.
[102] Kang JH, Sheu JJ, Kao S, Lin HC. Increased risk of multiple sclerosis following herpes zoster: a nationwide, population-based study. J Infect Dis 2011;204:188–92.
[103] Mahalingam R, Gershon A, Gershon M, Cohen JI, Arvin A, Zerboni L, et al. Current in vivo models of varicella-zoster virus neurotropism. Viruses 2019;11(6):E502.