Vitamin D, Epstein-Barr virus, and endogenous retroviruses in multiple sclerosis - facts and hypotheses

Christine Brütting1, Gabriele I. Stangl1, Martin S. Staege2

1 Institute of Agricultural and Nutritional Sciences, Martin Luther University Halle-Wittenberg, Von-Danchelmann-Platz 2, 06120 Halle (Saale), Germany
2 Department of Surgical and Conservative Paediatrics and Adolescent Medicine, Martin Luther University of Halle-Wittenberg, Ernst-Grube-Straße 40, 06120 Halle (Saale), Germany
*Correspondence: christine.bruetting@landw.uni-halle.de (Christine Brütting)
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The pathogenesis of multiple sclerosis (MS) remains poorly understood. Presumably, MS is caused by multiple environmental, epigenetic, and genetic factors. Among them, human endogenous retroviruses (HERVs), Epstein-Barr virus (EBV) and vitamin D have been suggested to play a role in the pathogenesis and course of MS. Because vitamin D can affect the immune system and infections, it can be hypothesized that there is a close interplay between vitamins, EBV and ERV in the pathogenesis of MS. Here, we summarize the important data on vitamin D, including polymorphisms in genes related to vitamin D metabolism, EBV and ERV, in the pathogenesis of MS and create hypotheses regarding their interactions. Data indicate that vitamin D has a strong impact on viral infections and interferes with EBV infection, while EBV is capable of activating silent ERVs. We believe that EBV could be the missing link between vitamin D and ERV in MS pathogenesis.

Keywords
Epstein-Barr virus (EBV); Genetic polymorphisms; Human endogenous retroviruses (HERVs); Vitamin D

1. Introduction

Although MS is one of the most common neurological diseases worldwide, its pathogenesis is still largely unknown. Dysregulation of the immune system has been discussed [1], as well as other endogenous and environmental factors, including endogenous retroviruses (ERV) [2], vitamin D levels [3], herpesviruses [4] such as Epstein-Barr virus (EBV) [5], the gut microbiota [6], short-chain fatty acids [7], smoking [8] and body mass index [9].

Here, we provide a short overview regarding the putative role of ERV, EBV and vitamin D and the interplay between these factors in the pathogenesis of MS. We included data from Mendelian randomization studies on vitamin D that investigated associations of genetic polymorphisms in genes related to vitamin D metabolism and susceptibility to MS. Finally, we aim to shed more light on the interconnected role of ERV, EBV and vitamin D in the pathogenesis of MS.

2. Multiple sclerosis and ERV

During evolution, the infection of germline cells with retroviruses led to accidental stable integration of these viruses into the genome of the infected host. These so-called endogenous retroviruses (ERV) are present in the genomes of virtually all animals. Approximately 8% of human DNA comprises ERV sequences. Complete ERVs are composed of four major structural genes: gag (encoding matrix and retroviral core), pol (reverse transcriptase and integrase), pro (protease), and env (envelope). Indeed, most human ERVs (HERVs) are not capable of replicating due to their high susceptibility to mutations [10]. However, some HERV elements contain intact open reading frames and can thus code for proteins [11]. It is possible that approximately 7% of all HERV sequences are transcriptionally active [12]. HERVs belong to so-called retroelements, which are mobile fragments that use an RNA intermediate. HERVs have regulatory long terminal repeats (LTR). These LTRs can be involved in the expression of ERV-derived sequences or can support the expression of neighboring genes [13, 14]. For example, HERV-W elements affect the transcription of at least 55 genes [15].

ERVs contribute to some important physiological functions, e.g., placental development [16], and they occasionally shelter the host from external viruses [17]. In addition, HERVs seem to be related to certain diseases [18], e.g., diabetes mellitus type I [19], schizophrenia and bipolar disorder [20], or cancer [21].

The first connection between HERV and MS was found in 1989, when the transcriptional activity of retroviruses in MS patients was found [22]. The respective HERV has been referred to as multiple sclerosis-associated retrovirus (MSRV) and is currently classified as HERV-W. In addition, several other HERVs seem to be associated with MS, such as HERVK-18 [23], HRES-1 [24] or HERVFc-1 [25, 26]. It is striking that the number of expressed HERV sequences is higher in MS patients than in healthy subjects [27], and HERV upregulation within MS plaques correlates with dis-
ease activity [28]. In addition, MS patients show higher antibody reactivity to certain HERV sequences [29]. HERV reactivation can lead to demyelinating plaques by initiating microglial inflammation [30]. For example, MSRV induces the release of the cytokines IL-6 and IL-8 [31].

Interestingly, women have higher levels of MSRV DNA copies than men, both in MS patients and controls [32], and the prevalence of MS is higher in women than in men [33]. When patients suffering from MS undergo antiretroviral therapy, symptoms of the disease can temporarily disappear [34–36], suggesting a strong association between HERV and MS. Indeed, these effects have been reported only in single cases and are, therefore, difficult to interpret in the context of a complex disease such as MS. However, the LTR sequences of some HERVs show polymorphisms that are typical for MS patients, and these polymorphisms might explain the epidemiology of MS in certain populations [37]. Notably, not all individuals have the same set of HERV copies [38]. Such insertional polymorphisms might influence susceptibility to MS development. Moreover, we observed an enrichment of HERV-like sequences near MS-related single-nucleotide polymorphisms (SNPs) [39]. The presence or absence of specific HERV sequences might indicate genetic factors that predispose patients to MS. However, genetic determinants alone cannot explain disease development. This is evident by the low heritability of MS, as only a minority of monozygotic twins are concordant for MS [40]. Therefore, it can be assumed that environmental factors are necessary for disease development. Vitamin D could be one of these factors.

3. Multiple sclerosis and vitamin D

Vitamin D is a group of fat-soluble secosteroids and is mainly synthesized by the skin after sunlight exposure [41]. Vitamin D deficiency is prevalent in many parts of the world [42] and affects approximately one billion people worldwide [43]. Although vitamin D is mainly associated with the regulation of calcium balance, it also has immunomodulatory effects and appears to beneficially impact respiratory infections [44, 45].

Low-vitamin D status is also associated with MS [46, 47]. Moreover, children born in autumn have a lower risk of developing MS than those born in spring [48, 49]. Since vitamin D status is usually higher at the end of summer than at the end of winter, we hypothesize a link between vitamin D and MS risk in children. The higher global prevalence of MS in countries distant from the equator, including MS patients did not find consistent or convincing effects of vitamin D supplementation on the MS course [64]. As mentioned above, genetic factors are unlikely to explain MS susceptibility. Today, it is not possible to exclude that a combination of vitamin D deficiency and genetic factors influencing vitamin D metabolism might be responsible for MS. The similarity of vitamin D concentrations was shown to be significantly greater in monozygotic twins than in dizygotic twins [65]. However, in this study, vitamin D was not an independent risk factor for MS. A major problem for the interpretation of such data is the fact that it is unclear at which time in life vitamin D deficiency might be required for MS development. An interesting recent study investigated differences in immune cell composition between MS-affected monozygotic twins and their healthy cotwins [66]. This study demonstrated that immune cell composition in twins is highly similar, independent of disease status. Interestingly, the similarity was higher in pairs where the healthy cotwin showed signs of subclinical neuroinflammation. A possible interpretation of this observation is that the interaction of the immune system with exogenous or endogenous antigens has taken place. In this regard, the influence of vitamin D on infections with exogenous viruses seems interesting.
4. Vitamin D and viruses

Vitamin D seems to have a great impact on viral infections. In epidemiological studies, lower serum vitamin D concentrations are associated with higher rates of infection with respiratory syncytial virus [67], polyomavirus [68], human papillomavirus [69], cytomegalovirus [70], and herpes simplex virus [71]. In addition, lower serum vitamin D concentrations are associated with EBV [72] and hepatitis C virus [73]. Additionally, vitamin D deficiency can induce higher hepatitis B virus levels [74] or a shorter survival time in patients with human immunodeficiency virus [75].

Vitamin D receptor polymorphisms are related to hepatitis B virus [76], hepatitis C virus [73], and the presence of respiratory syncytial virus infections [77]. In addition, in cell culture studies, vitamin D supplementation suppresses replication of human immunodeficiency virus in T-cells [78] and replication of rhinovirus in cells from patients with cystic fibrosis [79]. In vivo, vitamin D supplementation suppresses the replication of influenza virus in mice [80].

Interestingly, some of these vitamin D-affected viruses are able to activate silent HERVs. Such viruses include herpes simplex virus [81], influenza virus [82] and EBV [83]. In addition, the involvement of EBV infection in MS has been discussed for a long time, as the disease frequently develops shortly after infection with EBV [84].

5. Hypothesis on the interplay between vitamin D, ERV and EBV

To date, it remains unclear whether there is an association between vitamin D and HERV in MS pathogenesis. Recent data show a negative association between HERV and circulating vitamin D in MS patients [85]. Vitamin D downregulated ERV3 in a leukemia model [86]. In addition, ERVK LTRs have several intact and conserved binding sites for VDR receptors [87].

Interestingly, vitamin D levels are inversely correlated with EBV load in MS patients [88]. As mentioned above, EBV has been shown to be able to transactivate HERV, with potential superantigen activity [83]. EBV is the causative virus for infectious mononucleosis, and patients with infectious mononucleosis have lower levels of vitamin D [89]. EBV infects B cells and immortalizes these cells into so-called lymphoblastoid cell lines. In vivo, a strong immune response against EBV inhibits the proliferation of lymphoblastoid cell lines in immunocompetent hosts. Recently, it was shown that humanized mice carrying the major MS risk allele HLA-DRB1*15:01 were not able to adequately control EBV infection [90]. This gives a direct link between the exogenous factor EBV and an immunologically relevant MS-associated polymorphism. EBV is usually acquired early in life and persists throughout the lifespan in infected individuals. Interestingly, EBV-encoded nuclear antigen 2, a master regulator of EBV-driven B cell immortalization, has overlapping DNA binding sites with the vitamin D receptor [91]. It is likely that at high vitamin D levels, the vitamin D receptor out-competes EBNA2 for DNA binding, which can explain the inverse correlation between vitamin D levels and EBV. This also reduces the expression of HERV, which is transactivated by EBV. In addition to EBNA2, the vitamin D receptor can bind EBNA3 (reviewed in [92]). This binding inhibits binding of the vitamin D receptor to target genes. Consequently, at high levels of EBV nuclear antigen expression and low vitamin D, EBV target genes, including transactivated HERV, can be activated, whereas at higher vitamin D levels, this transactivation is inhibited. The reduced anti-EBNA-1 antibody levels in MS patients after vitamin D supplementation could be due to the general anti-inflammatory effect of vitamin D [93, 94]. EBV is polymorphic [95], and it has not been elucidated whether all EBV variants have the same transactivation activity for HERV. The vast majority of adult individuals worldwide are latently infected with EBV. Polymorphisms in EBV, variable activity of EBV-interfering pathways such as the vitamin D pathway, and polymorphisms in ERV and HERV-like genetic elements might explain the observation that only a minority of EBV-infected individuals develop MS.

6. Conclusions

Several risk factors for MS have been described, including polymorphisms in immunologically relevant genes, as well as environmental factors such as EBV and vitamin D. In addition, endogenous retrovirus activation has been linked to MS. Recent observations suggest that all these factors are linked together. A possible model implies that the balance between EBV nuclear antigens and activated vitamin D receptors can be shifted towards activation of HERV (low vitamin D, high EBV antigen expression) or inhibition of HERV activation (high vitamin D, low or absent EBV antigens). Direct HERV-mediated toxicity or aberrant immune activation by HERV components can then induce MS. This model suggests multiple therapeutic targets (EBV, HERV, vitamin D metabolism), and elucidation of the exact interplay between these factors might lead to new treatment strategies for MS.

Author contributions
All authors wrote the paper with input from all authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate
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Conflict of interest

The authors have declared no conflict of interest.

References

[1] Nicol B, Salou M, Laplau DA, Wekerle H. The autoimmune concept of multiple sclerosis. La Presse Médicale. 2015; 44: e103-e112.
[2] Bhetaiyra PJ, Kriessel JD, Fischer KF. Analysis of human endogenous retrovirus expression in multiple sclerosis plaques. The Journal of Emerging Diseases and Virology. 2017; 3: 1-17.
[3] Bärrnhielm M, Hedström AK, Kockum I, Sundqvist E, Gustafsson SA, Hillert J, et al. Sunlight is associated with decreased multiple sclerosis risk: no interaction with human leukocyte antigen-DRB1*15. European Journal of Neurology. 2012; 19: 955-962.
[4] Pormohammad A, Azimi T, Falah F, Faghilho E. Relationship of human herpes virus 6 and multiple sclerosis: a systematic review and meta-analysis. Journal of Cellular Physiology. 2018; 233: 2830-2862.
[5] Jacobs BM, Giovannoni G, Cuzick J, Dobson R. Systematic review and meta-analysis of the association between Epstein-Barr virus, multiple sclerosis and other risk factors. Multiple Sclerosis Journal. 2020; 26: 1281-1297.
[6] Adamsczyk-Sowa M, Medrek A, Madaj P, Michlicka W, Dobrakovski P. Does the gut microbiota influence immunity and inflammation in multiple sclerosis pathophysiology? Journal of Immunology Research. 2017; 2017: 7904821.
[7] Duscha A, Gisevius B, Hirschberg S, Yissachar N, Stangl GI, Eilers E, et al. Propionic acid shapes the multiple sclerosis disease course by an immunomodulatory mechanism. Cell. 2020; 180: 1067-1080.
[8] Arneb B. Multiple sclerosis and smoking. American Journal of Medicine. 2020; 133: 783-788.
[9] Vandebergh M, Goris A. Smoking and multiple sclerosis risk: a Mendelian randomization study. Journal of Neurology. 2020; 267: 3083-3091.
[10] Jern P, Coffin JM. Effects of retroviruses on host genome function. Annual Review of Genetics. 2008; 42: 709-732.
[11] Dupressoir A, Lavialle C, Heidmann T. From ancestral infectious retroviruses to bona fide cellular genes: role of the captured syncytins in placentation. Placenta. 2012; 33: 663-671.
[12] Oja M, Peltonen J, Blomberg J, Kaski S. Methods for estimating human endogenous retrovirus activities from EST databases. BMC Bioinformatics. 2007; 8: S11.
[13] Landry JR, Mager DL. Functional analysis of the endogenous retroviral promoter of the human endothelin B receptor gene. Journal of Virology. 2003; 77: 7459-7466.
[14] Buzdin A, Kovalskaya-Alexandrova E, Gogvadze E, Sverdlov E. At least 50% of human-specific HERV-K (HML-2) long terminal repeat sequences serve in vivo as active promoters for host nonrepetitive DNA transcription. Journal of Virology. 2006; 80: 10752-10762.
[15] Grandi N, Cadeddu M, Blomberg J, Tramontano E. Contribution of type W human endogenous retroviruses to the human genome: characterization of HERV-W proviral insertions and processed pseudogenes. Retrovirology. 2016; 13: 67-92.
[16] Mi S, Lee X, Li XP, Veldman GM, Finnerty H, Racie L, et al. Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. Nature. 2000; 403: 785-789.
[17] Varella M, Spencer TE, Palmarini M, Arnaud F. Viruses: the special relationship between endogenous retroviruses and their host. Annals of the New York Academy of Sciences. 2009; 1178: 157-172.
[18] Dolei A. Endogenous retroviruses and human disease. Expert Review of Clinical Immunology. 2006; 2: 149-167.
[19] Mason MJ, Speake C, Gersuk VH, Nguyen QA, O'Brien KK, Odegard JM, et al. Low HERV-K (C4) copy number is associated with type 1 diabetes. Diabetes. 2014; 63: 1789-1795.
[20] Perron H, Hamdani N, Faucard R, Lajmef M, Jamain S, Daban-Huard C, et al. Molecular characteristics of Human Endogenous Retrovirus type-W in schizophrenia and bipolar disorder. Translational Psychiatry. 2012; 2: e201.
[21] Goering W, Schmitt K, Dostert M, Schaal H, Deenen R, Mayer J, et al. Human endogenous retrovirus HERV-K (HML-2) activity in prostate cancer is dominated by a few loci. The Prostate. 2015; 75: 1958-1971.
[22] Perron H, Garson JA, Bedin F, Beseme F, Pananos-Baccala G, Komurian-Pradel F, et al. Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94: 7583-7588.
[23] Tai AK, O’Reilly EJ, Alroy KA, Simon KC, Munger KL, Huber BT, et al. Human endogenous retrovirus-K18 Env as a risk factor in multiple sclerosis. Multiple Sclerosis Journal. 2008; 14: 1175-1180.
[24] Rasmussen HB, Kelly MA, Francis DA, Clausen J. Association between the endogenous retrovirus HRES-1 and multiple sclerosis in the United Kingdom—evidence of genetically different disease subsets? Disease Markers. 2000; 16: 101-104.
[25] Nexø BA, Christensen T, Frederiksen J, Møller-Larsen A, Oturai AB, Villesen P, et al. The etiology of multiple sclerosis: genetic evidence for the involvement of the human endogenous retrovirus HERV-Fc1. PLoS ONE. 2011; 6: e16652.
[26] De la Hera B, Varade J, García-Montojo M, Alcina A, Fedetz M, Alloza I, et al. Human endogenous retrovirus HERV-Fc1 association with multiple sclerosis susceptibility: a meta-analysis. PLoS ONE 2014; 9: e90182.
[27] Garcia-Montojo M, Rodríguez-Martín E, Ramos-Mozo P, Ortega-Madueño I, Domínguez-Mozo MI, Arias-Leal A, et al. Syncytin-1/HERV-W envelope is an early activation marker of leukocytes and is upregulated in multiple sclerosis patients. European Journal of Immunology. 2020; 50: 685-694.
[28] Mameli G, Astone V, Arru G, Marconi S, Lovato L, Serra C, et al. Brains and peripheral blood mononuclear cells of multiple sclerosis (MS) patients hypersynthesize MS-associated retrovirus/HERV-W endogenous retrovirus, but not Human herpesvirus 6. Journal of General Virology. 2007; 88: 264-274.
[29] Christensen T, Petersen T, Thiel S, Brudek T, Ellermann-Eriksen S, Møller-Larsen A. Gene-environment interactions in multiple sclerosis: innate and adaptive immune responses to human endogenous retrovirus and herpesvirus antigens and the lectin complement activation pathway. Journal of Neuroimmunology. 2007; 183: 175-188.
[30] Arneb B. Up-to-date knowledge about the association between multiple sclerosis and the reactivation of human endogenous retrovirus infections. Journal of Neurology. 2018; 265, 1733-1739.
[31] Duperray A, Barbe D, Raguenez G, Wekler BB, Romero IA, Couraud PO, et al. Inflammatory response of endothelial cells to a human endogenous retrovirus associated with multiple sclerosis is mediated by TLR4. International Immunology. 2015; 27: 545-553.
[32] Garcia-Montojo M, Domínguez-Mozo M, Arias-Leal A, Garcia-Martínez A, De las Heras V, Casanova I, et al. The DNA copy number of human endogenous retrovirus-W (MSRV-type) is increased in multiple sclerosis patients and is influenced by gender and disease severity. PLoS ONE. 2013; 8: e53623.
[33] Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al. Cognition in multiple sclerosis: state of the field and priorities for the future. Neurology. 2018; 90: 278-288.
[34] Maruszak H, Brew BJ, Giovannoni G, Gold J. Could antiretroviral drugs be effective in multiple sclerosis? A case report. European Journal of Neurology. 2011; 19: e110-e111.
[35] Chalkley J, Berger JR. Multiple sclerosis remission following antiretroviral therapy in an HIV-infected man. Journal of Neurology. 2014; 20: 640-643.
[36] Mauclu F, Schluep M, Granzierra C. Sustained disease-activity-free status in a woman with relapsing-remitting multiple sclerosis treated with antiretroviral therapy for Human Immunodeficiency Virus type 1 infection. Journal of Multiple Sclerosis. 2015; 2: 2-4.
Clausen J. Endogenous retroviruses and MS: using ERVs as disease markers. International MS Journal. 2003; 10: 22-28.

Turner G, Barbulescu M, Su M, Jensen-Seaman M, Kidd KK, Lenz J. Insertional polymorphisms of full-length endogenous retroviruses in humans. Current Biology. 2001; 11: 1531-1535.

Böttiger C, Emmer A, Kornhuber M, Staeger MS. A survey of endogenous retrovirus (ERV) sequences in the vicinity of multiple sclerosis (MS)-associated single nucleotide polymorphisms (SNPs). Molecular Biology Reports. 2016; 43: 827-836.

Ebers GC, Bulman DE, Sadovnick AD, Paty DW, Warren S, Hader W, et al. A population-based study of multiple sclerosis in twins. The New England Journal of Medicine. 1986; 315: 1638-1642.

Mason RS. Vitamin D: new insights into an old secosteroid. Asian Pacific Journal of Clinical Nutrition. 2005; 14: S19.

Amrein K, Scherkl M, Hoffmann M, Neuwrosch-Sommerregger S, Köstenberger M, Berisha AT, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. European Journal of Clinical Nutrition. 2020; 74: 1498-1513.

Nair R, Maseeh A. Vitamin D: the “sunshine” vitamin. Journal of Pharmacology & Pharmacotherapeutics. 2012; 3: 118-126.

Carmeliet G, Dermauw V, Bouillon R. Vitamin D signaling in calcium and bone homeostasis: a delicate balance. Best Practice & Research Clinical Endocrinology & Metabolism. 2015; 29: 621-631.

Mareczek F, Bechthold A, Egert S, Ernst JB, Melo van Lent D, Pilz S, et al. Role of vitamin D in preventing and treating selected extraskelatal diseases—an umbrella review. Nutrients. 2020; 12: 969.

Rhead B, Bärnhielm M, Gianfrancesco M, Mok A, Shao X, Quach H, et al. Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk. Neurology: Genetics. 2016; 2: e97.

Nielsen NM, Munger KL, Koch-Henriksen N, Hougaard DM, Magyari M, Jørgensen KT, et al. Neonatal vitamin D status and risk of multiple sclerosis: a population-based case-control study. Neurology. 2017; 88: 44-51.

Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC. Timing of birth and risk of multiple sclerosis: population based study. British Medical Journal. 2005; 330: 120.

Dobson R, Giovanni G, Ramagopalan S. The month of birth effect in multiple sclerosis: systematic review, meta-analysis and effect of latitude. Journal of Neurology, Neurosurgery, and Psychiatry. 2013; 84: 427-432.

Simpson S, Blizzard L, Othahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. Journal of Neurology, Neurosurgery, and Psychiatry. 2011; 82: 1132-1141.

Gale CR, Martyn CN. Migrant studies in multiple sclerosis. Progress in Neurobiology. 1995; 47: 425-448.

Heidari B, Mirghassemi MBH. Seasonal variations in serum vitamin D according to age and sex. Caspian Journal of Internal Medicine. 2012; 3: 535-540.

Mattorzi C, Paolino G, Salvi M, Macaluso L, Luci C, Morrone S, et al. Peripheral blood regulatory T cell measurements correlate with serum vitamin D level in patients with psoriasis. Age. 2016; 56: 23-85.

Abdollahi E, Rezaee SA, Saghaﬁ N, Rastin M, Clifton V, Sabehkar A, et al. Evaluation of the effects of 1, 25 vitamin D3 on regulatory T cells and T helper 17 cells in vitamin D-deﬁcient women with unexplained recurrent pregnancy loss. Current Molecular Pharmacology. 2020; 13: 306-317.

Ramagopalan SV, Maugeri NJ, Handunnetthi L, Lincoln MR, Orton SM, Dyment DA, et al. Expression of the multiple sclerosis-associated MHC class II allele HLA-DRB1*1501 is regulated by vitamin D. PLoS Genetics. 2009; 5: e1000369.

Calton EK, Keane KN, Newsholme P, Soares IM. The impact of vitamin D levels on inflammatory status: a systematic review of immune cell studies. PLoS ONE. 2015; 10: e0141770.

Wagner CA, Roqué PJ, Goverman JM. Pathogenic T cell cytokines in multiple sclerosis. Journal of Experimental Medicine. 2020; 217: e20190460.

Simpson Jr S, Taylor B, Blizzard L, Ponsonby AL, Pittas F, Tremlett H, et al. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. Annals of Neurology. 2010; 68: 193-203.

Patsopoulos NA, Baranzini SE, Santaniello A, Shoostari P, Cotsapas C, Wong G, et al. The Multiple Sclerosis Genomic Map: role of peripheral immune cells and resident microglia in susceptibility. BioRxiv. 2017; 143933.

Imani D, Razi B, Motallebnezhad M, Rezaei R. Association between vitamin D receptor (VDR) polymorphisms and the risk of multiple sclerosis (MS): an updated meta-analysis. BMC Neurology. 2019; 19: 339.

Graves JS, Barcellos LF, Krupp L, Belman A, Shao X, Quach H, et al. Vitamin D genes influence MS relapses in children. Multiple Sclerosis Journal. 2020; 26: 894-901.

Agnello L, Szacczone C, Lo Sasso B, Ragonese P, Milano S, Salemi G, et al. CYP27A1, CYP24A1, and XRRA-alpha polymorphisms, vitamin D, and multiple sclerosis: a pilot study. Journal of Molecular Neuroscience. 2018; 66: 77-84.

AL-Eitan L, Qudah MA, Qawasmeh MA. Association of multiple sclerosis phenotypes with single nucleotide polymorphisms of IL7R, LAG3, and CD40 genes in a Jordanian population: a genotype-phenotype study. Biomolecules. 2020; 10: 356.

Smolders J, Torkildsen Ø, Camu W, Holmøy T. An update on vitamin D and disease activity in multiple sclerosis. CNS drugs. 2019; 33: 1187-1199.

Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, Chao MJ, et al. Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. The American Journal of Clinical Nutrition. 2008; 88: 441-447.

Gerdès LA, Janoschka C, Eveslage M, Mannig B, Wirth T, Schulte-Mecklenbeck A, et al. Immune signatures of promordial multiple sclerosis in monozygotic twins. Proceedings of the National Academy of Sciences. 2020; 117: 21546-21556.

Tüfekçi S, Aygün E. Association of vitamin D deficiency and respiratory syncytial virus with severe lower respiratory tract infection in newborn intensive care unit. 2020. (in preparation)

Rech MA, Fleming JN, Moore CL. 25-hydroxyvitamin D deficiency and opportunistic viral infections after kidney transplant. Experimental and Clinical Transplant. 2014; 12: 95-100.

Shim J, Pérez A, Symanski E, Nyitray AG. Association between serum 25-hydroxyvitamin D level and human papillomavirus cervical infection in women in the United States. The Journal of Infectious Diseases. 2016; 213: 1886-1892.

van Dijk L, Blinkense O, Alm J, Björklund A, Malmberg KJ, Mogujiakakos D, et al. Increased incidence of chronic GVHD and CMV disease in patients with vitamin D deficiency before allogeneic stem cell transplantation. Bone Marrow Transplantation. 2015; 50: 1217-1223.

Öztękin A, Öztekin C. Vitamin D levels in patients with recurrent herpes labialis. Viral Immunology. 2019; 32: 258-262.

Zwart SR, Mehta SK, Ploutz-Snyder R, Bourbeau Y, Locke JP, Pierson DL, et al. Response to vitamin D supplementation during Antarctic winter is related to BMI, and supplementation can mitigate Epstein-Barr virus reactivation. The Journal of Nutrition. 2011; 141: 692-697.

Abdel-Mohsen MA, El-Braky AAA, Ghazal AAER, Shamsey MM. Autophagy, apoptosis, vitamin D, and vitamin D receptor in hepatocellular carcinoma associated with hepatitis C virus. Medicine. 2018; 97: e0172.

Hoan NX, Khuyn H, Binh MT, Giang DP, Van Tong H, Hoan PQ, et al. Association of vitamin D deficiency with hepatitis B virus-related liver diseases. BMC infectious diseases. 2016; 16: 507.

Haug C, Müller F, Aukrust P, Freldal SS. Subnormal serum concentration of 1, 25-vitamin D in human immunodeficiency virus infection: correlation with degree of immune deficiency and survival. Journal of Infectious Diseases. 1994; 169: 889-893.
He Q, Huang Y, Zhang L, Yan Y, Liu J, Song X, et al. Association between vitamin D receptor polymorphisms and hepatitis B virus infection susceptibility: a meta-analysis study. Gene. 2018; 645: 105-112.

Laplana M, Royo JL, Fliba J. Vitamin D receptor polymorphisms and risk of enveloped virus infection: a meta-analysis. Gene. 2018; 678: 384-394.

Aguilar-Jimenez W, Villegas-Ospina S, Gonzalez S, Zapata W, Saulle I, Garziano M, et al. Precursor forms of vitamin D reduce HIV-1 infection in vitro. Journal of Acquired Immune Deficiency Syndromes. 2016; 73: 497-506.

Schögler A, Muster RJ, Kieninger E, Casaulta C, Tapparel C, Jung A, et al. Vitamin D represses rhinovirus replication in cystic fibrosis cells by inducing LL-37. European Respiratory Journal. 2016; 47: 520-530.

Hayashi H, Okamatsu M, Ogasawara H, Tsugawa N, Isoda N, Matsuno K, et al. Oral supplementation of the vitamin D metabolite 25(OH)D3 against influenza virus infection in mice. Nutrients. 2020; 12: 2000.

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

Ricigliano VA, Handel AE, Sandve GK, Annibali V, Ristori G, Mechelli R, et al. EBNA2 binds to genomic intervals associated with multiple sclerosis and overlaps with vitamin D receptor occupancy. PLoS ONE. 2015; 10: e0119605.

Marcucci SB, Obeidat AZ, EBNA1, EBNA2, and EBNA3 link Epstein-Barr virus and hypovitaminosis D in multiple sclerosis pathogenesis. Journal of Neuroimmunology. 2020; 339: 577116.

Rolsa E, Lossius A, Abdelmagid N, Lindstrom JC, Kampman MT, Jørgensen L, et al. Effect of high-dose vitamin D3 supplementation on antibody responses against Epstein-Barr virus in relapsing-remitting multiple sclerosis. Multiple Sclerosis Journal. 2017; 23: 395-402.

Bernig T, Richter N, Volkmer I, Staeg E. Functional analysis and molecular characterization of spontaneously outgrown human lymphoblastoid cell lines. Molecular Biology Reports. 2014; 41: 6993-7007.