Linfomas podem ser provocados pelo vírus de Epstein Barr

Epstein-Barr Virus Causes Lymphomas

Retirado de :
http://www.smokershistory.com/EBVlymph.html

EBV has been declared a Class I human carcinogen by the IARC. (Epstein Barr Virus and Kaposi’s Sarcoma Herpesvirus/Human Herpesvirus 8. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans). IARC Monograph 70. Lyon: International Agency for Research on Cancer; 1997.)

"5.5 Evaluation. There is sufficient evidence for the carcinogenicity of EBV in the causation of Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppression-related lymphoma, Hodgkin's disease and nasopharyngeal carcinoma."

"EBV is carcinogenic to humans (Group I)."

IARC Monograph 70, Epstein-Barr Virus, summary (1997) / IARC (pdf, 10 pp)

Reviews

Epstein-Barr virus, infectious mononucleosis, Burkitt's lymphoma and nasopharyngeal carcinoma. G Klein. Israel J Med Sci 1977 Jul;13(7):716-724. "The timing and extent of seroconversion are strongly related to socioeconomic status. In low socioeconomic groups, infection occurs during early childhood, as a rule. It is not accompanied by any recognized disease, and the route of transmission is unknown. Only a minority of children become infected in high socioeconomic groups where a later infection, during the teens, predominates."
The spectrum of Epstein-Barr virus-associated lymphoproliferative disease in Korea: incidence of disease entities by age groups. EY Cho, KH Kim, WS Kim, KH Yoo, HH Koo, YH Ko. J Korean Med Sci 2008 Apr;23(2):185-192. "T or NK cell NHLs were the most common forms of EBV-positive NHLs (107/167, 64%); among these, nasal-type NK/T cell lymphomas were the most common (89/107, 83%). According to the age, Burkitt's lymphoma was the most common in early childhood; in teenagers, chronic (active) EBV infection-associated LPD was the most common type. The incidence of NK/T cell lymphoma began to increase from the twenties and formed the major type of EBV-associated tumor throughout life. Diffuse large B cell lymphoma formed the major type in the sixties and seventies."


Strain Differences

Epstein-Barr virus latent gene sequences as geographical markers of viral origin: unique EBNA3 gene signatures identify Japanese viruses as distinct members of the Asian virus family. A Sawada, D Croom-Carter, O Kondo, M Yasui, M Koyama-Sato, M Inoue, K Kawa, AB Rickinson, RJ Tierney. J Gen Virol 2011 May;92(Pt 5):1032-1043. "Thus, while Chinese viruses mainly fall into two families with strongly linked 'Wu' or 'Li' alleles at EBNA2 and EBNA3A/B/C, Japanese viruses all have the consensus Wu EBNA2 allele but fall into two families at EBNA3A/B/C. One family has variant Li-like sequences at EBNA3A and 3B and the consensus Li sequence at EBNA3C; the other family has variant Wu-like sequences at EBNA3A, variants of a low frequency Chinese allele 'Sp' at EBNA3B and a consensus Sp sequence at EBNA3C. Thus, EBNA3A/B/C allelotypes clearly distinguish Japanese from Chinese strains. Interestingly, most Japanese viruses also lack those immune-escape mutations in the HLA-A11 epitope-encoding region of EBNA3B that are so characteristic of viruses from the highly A11-positive Chinese population."

EBV and Hodgkin's Disease

established an association of Hodgkin's disease with Epstein-Barr virus. Recently, Epstein-Barr virus genomes and gene products have been detected in the neoplastic cells of approximately 50% of cases, most notably the latent membrane protein, which has transforming potential."


Risk factors for Hodgkin's disease by Epstein-Barr virus (EBV) status: prior infection by EBV and other agents. FE Alexander, RF Jarrett, D Lawrence, AA Armstrong, J Freeland, DA Gokhale, E Kane, GM Taylor, DH Wright, RA Cartwright. Br J Cancer 2000 Mar;82(5):1117-1121. 19/103 tumors were EBV+. History of infectious mononucleosis & Hodgkin's disease, OR= 2.43 (95% CI= 1.10-5.33); history of IM and EBV-positive HD, OR= 9.16 (95% CI= 1.07-78.31).

Alexander - Br J Cancer 2000 abstract / PubMed

The correlation of Epstein-Barr virus expression and lymphocyte subsets with the clinical presentation of nodular sclerosing Hodgkin disease. A Kandil, S Bazarbashi, WA Mourad. Cancer 2001 Jun 1;91(11):1957-1963. EBV expression was seen in 24 (50%) cases.

Kandil - Cancer 2001 abstract / PubMed

South Asian ethnicity and material deprivation increase the risk of Epstein-Barr virus infection in childhood Hodgkin's disease. KJ Flavell, JP Biddulph, JE Powell, SE Parkes, D Redfern, M Weinreb, P Nelson, JR Mann, LS Young, PG Murray. Br J Cancer 2001 Aug;85(3):350-356. "62% of [55] cases were Epstein-Barr virus-positive... The relative risk of Epstein-Barr virus-positivity showed a gradient with increasing Townsend score; the risk being 7-times higher in the most deprived quartile compared with the least deprived group."

Flavell - Br J Cancer 2001 abstract / PubMed

Epstein-Barr virus (EBV) in Chinese pediatric Hodgkin disease: Hodgkin disease in young children is an EBV-related lymphoma. XG Zhou, K Sandvej, PJ Li, XL Ji, QH Yan, XP Zhang, JP Da, SJ Hamilton-Dutoit. Cancer 2001 Sep 15;92(6):1621-1631. In 104 pediatric and 52 adult Chinese HD cases, "EBV was identified in tumor cells in 113 of 156 (72%) HD cases but was more frequent in pediatric cases (93 of 104; 89%) compared with adult cases (20 of 52; 38%) (P < 0.01; chi-square test). EBV was found in 86 out of 91 (95%) cases in children aged 3-10 years and in 7 out of 13 (54%) cases in children aged 11-14 years (P < 0.01; chi-square test). The authors believe that pediatric HD now should be regarded as a distinctive EBV-related lymphoma."

Zhou - Cancer 2001 abstract / PubMed

A defective, rearranged Epstein-Barr virus genome in EBER-negative and EBER-positive Hodgkin's disease. YJ Gan, BI Razzouk, T Su, JW Sixbey. Am J Pathol 2002 Mar;160(3):781-786. "The Epstein-Barr virus (EBV) has been linked to approximately half the cases of Hodgkin’s disease (HD), with virus localized by EBER in situ hybridization to the malignant Reed-Sternberg cell that characteristically makes up less
than 1% of the tumor mass. Recent descriptions of relapsed HD, shown to be EBV-positive at initial diagnosis but EBV-negative on reoccurrence, raise the possibility of viral DNA loss during tumor progression in some individuals." 8/24 EBER-negative HD had PCR evidence of defective EBV DNA. "Detection of defective EBV genomes with the potential to disrupt viral gene regulation suggests one mechanism for pathogenic diversity that may also account for loss of prototypic EBV from individual tumor cells."

Gan - Am J Pathol 2002 abstract / PubMed
Gan - Am J Pathol 2002 Full Article

Epstein-Barr virus in Hodgkin's disease: the example of central Tunisia. S Korbi, M Trimeche, B Sriha, MT Yacoubi, S Hmissa, M Mokni, P Delvenne, J Boniver, S Rammeh. Ann Pathol 2002 Apr;22(2):96-101. EBV early RNA transcripts (EBER) was detected in 70% of 77 cases.

Korbi - Ann Pathol 2002 abstract / PubMed

Hematopoietic and lymphatic cancers in relatives of patients with infectious mononucleosis. H Hjalgrim, K Rostgaard, J Askling, M Madsen, HH Storm, CS Rabkin, M Melbye. J Natl Cancer Inst 2002 May 1;94(9):678-681. "The unremarkable risk for Hodgkin's lymphoma in family members of patients with EBV-related infectious mononucleosis indicates that socioeconomic confounding is an unlikely explanation for the association between EBV-related infectious mononucleosis and Hodgkin's lymphoma."

Hjalgrim - JNCI 2002 abstract / PubMed
Hjalgrim - JNCI 2002 Full Article

Epstein-barr virus-associated non-Hodgkin's lymphoma of B-cell origin, Hodgkin's disease, acute leukemia, and systemic lupus erythematosus: a serologic and molecular analysis. W Mitarnun, J Pradutkanchana, S Takao, V Saechan, S Suwiwat, T Ishida. J Med Assoc Thai. 2002 May;85(5):552-9. In 58 patients, "EBV internal repeat-1 region (IR-1) in peripheral blood CD3+ cells was detected in 10 of 14 patients (71.5%) with NHL-B, 3 of 8 patients (37.5%) with Hodgkin's disease, 1 of 6 patients (16.7%) with acute leukemia, 4 of 9 patients (44.5%) with SLE, and was not detected in any of the 21 patients with other diseases."

Mitarnun 2002 abstract / PubMed


Longer failure-free survival interval of Epstein-Barr virus-associated classical Hodgkin's lymphoma: a single-institution study. J Krugmann, A Tzankov, A
"Latent membrane protein1 was detected in 31/119 (26%) classical Hodgkin's lymphoma, and Epstein-Barr virus subtyping was successful in 19 of the 31 virus-infected classical Hodgkin's lymphoma cases, as well as in 28 of 54 reactive tonsils. Subtype A was observed in all classical Hodgkin's lymphoma patients and in 26/28 (93%) tonsils. The 30-base pair latent membrane protein1 gene deletion was found in only 4/31 (13%) Epstein-Barr virus-associated classical Hodgkin's lymphoma as well as in 20/54 (37%) reactive tonsils."

Krugmann - Mod Pathol 2003 abstract / PubMed

"EBV LMP-1 was positive in 82 (82%) cases, most often in the nodular sclerosis subtype, 43 (86%) cases."

Karnik - Pathology 2003 abstract / PubMed

"We found an LMP-1 positive rate of 50% for 22 cases of HL and 35% for 63 cases of NHL. Among HL, 5 were children and 16 were adults, with LMP-1 positive rates of 60% and 50% respectively. Among NHL, 3 were children and 59 were adults, with equal LMP-1 positive rates of 33%.

Córdova Pérez - P R Health Sci J 2003 abstract / PubMed

"The H-RS cells of 62 classic Hodgkin lymphomas were... positive for both EBV latent membrane protein-1 and EBER in 37 (59.68%); there was complete concordance of results for EBV by both procedures."


"EBV-infected H&RS cells were detected in 9 of 10 cases of HL MC, 5 of 9 of HL-like ATLL and 2 of 10 HL NS.... 2 of 5 cases of HL-like ATLL with EBV infection and 2 of 2 HL NS with EBV had IP10/MIG-positive H&RS..."
cells. The chemokine expressions in H&RS cells seemed to be associated with EBV infection rather than histologic subtypes."

Ohshima - Int J Cancer 2003 abstract / PubMed

Comparison of Epstein-Barr virus presence in Hodgkin lymphoma in pediatric versus adult Argentine patients. E De Matteo, AV Barón, P Chabay, J Porta, M Dragosky, MV Preciado. Arch Pathol Lab Med 2003 Oct;127(10):1325-1329. 92 pediatric and 42 adult Hodgkin lymphoma cases from a public center, and 39 adult cases from a private center. "55% of the pediatric cases and 31% of the adult cases were positive [for Epstein-Barr encoded RNAs]. Among adult EBV+ cases, 38% were from the public hospital, and 23% were from the private center. EBV was present in 77% of the pediatric mixed cellularity Hodgkin lymphoma cases when compared with the other histologic subtypes of Hodgkin lymphoma. EBV was mainly detected in mixed cellularity cases (39% in the adult group)."

De Matteo - Arch Pathol Lab Med 2003 abstract / PubMed

The Scotland and Newcastle epidemiological study of Hodgkin's disease: impact of histopathological review and EBV status on incidence estimates. RF Jarrett, AS Krajewski, B Angus, J Freeland, PR Taylor, GM Taylor, FE Alexander. J Clin Pathol 2003 Nov;56(11):811-816. 622 HL patients. "EBV status was determined for 537 cases, including 461 cases with a review diagnosis of CHL; in 154 (33%) of these last cases all of the HRS cells were EBER positive... LMP1 staining identified no EBV+ HL cases that were not picked up using the EBER assay."

Jarrett - J Clin Pathol 2003 full article / PubMed Central

[Epstein-Barr virus presence in Colombian Hodgkin lymphoma cases and its relation to treatment response]. S Quijano, C Saavedra, S Fiorentino, O Orozco, MM Bravo. Biomedica 2004 Jun;24(2):163-173. Lymph nodes from 67 HL patients. "EBERs transcripts were found in 67% of the cases and LMP-1 in the Reed-Sternberg tumor cells at a 56.7% rate. The prevalence, as determined by histological subtype, was 69.81% for nodular sclerosing, 85.71% for mixed cellularity and 40% for lymphocyte-rich. Epstein-Barr virus presence was more frequent in children (84.2%) in comparison with adults (60.4%)."

Quijano - Biomedica 2004 abstract / PubMed

Epstein-Barr virus expression in Hodgkin's disease in Jordan. NM Almasri, HS Khalidi. Saudi Med J 2004 Jun;25(6):770-775. "Epstein Barr virus was seen in 47% of our cases: 22 (65%) of the 34 mixed cellularity and 8 (29%) of 28 nodular sclerosis HD. None of our 2 lymphocyte predominant HD cases showed evidence of EBV. Epstein-Barr virus was seen in 73% of HD cases in children below 15 years of age as opposed to 34% of the young adult group."

Almasri - Saudi Med J 2004 abstract / PubMed

Heterogeneity of risk factors and antibody profiles in epstein-barr virus genome-positive and -negative hodgkin lymphoma. ET Chang, T Zheng, ET Lennette, EG Weir,
M Borowitz, RB Mann, D Spiegelman, NE Mueller. J Infect Dis 2004 Jun 15;189(12):2271-2281. "EBV-positive patients were less educated and more likely to have smoked cigarettes and had more prevalent and higher EBV antibody titers, compared with EBV-negative patients."

Chang - J Infect Dis 2004 abstract / PubMed

Hodgkin's disease and association with Epstein-Barr virus in children in Southeast Turkey. F Yilmaz, AK Uzunlar, N Sogutcu, M Ozaydin. Saudi Med J 2005 Apr;26(4):571-575. "Epstein-Barr virus-LMP1 were positive in 31 cases (61.5%) of a total of 52 cases and the most were MC [mixed cellularity] (91.3%)."


Phenotype and frequency of Epstein-Barr virus-infected cells in pretreatment blood samples from patients with Hodgkin lymphoma. G Khan, A Lake, L Shield, J Freeland, L Andrew, FE Alexander, R Jackson, PR Taylor, EA McCruden, RF Jarrett. Br J Haematol 2005 May;129(4):511-519. "The frequency of circulating EBV-infected cells was significantly higher (P < 0.001) in pretreatment blood samples from EBV-associated cases when compared with non-EBV-associated cases."

Khan - Br J Haematol 2005 abstract / PubMed

Association of the Epstein-Barr viruses with Hodgkin lymphoma: an analysis of pediatric cases in Thailand. V Hemsrichart, J Pintong. J Med Assoc Thai 2005 Jun;88(6):782-787. "EBV encoded RNA by in situ hybridization was demonstrated in 92.8% of classic HL: 3 of 4 (75%) with nodular sclerosis; 9 of the 9 with mixed cellularity (100%) and 1 of 1 (100%) with lymphocyte depletion. Case of nodular lymphocyte predominance was negative for EBV..."

Hemsrichart & Pintong - J Med Assoc Thai 2005 abstract / PubMed

Impact of latent Epstein-Barr virus infection on outcome in children and adolescents with Hodgkin's lymphoma. A Claviez, M Tiemann, H Lüders, M Krams, R Parwaresch, G Schellong, W Dörffel. J Clin Oncol 2005 Jun 20;23(18):4048-4056. Eight hundred forty-two children and adolescents (median age, 13.7 years). "Two hundred sixty-three patients (31%) were LMP positive [by immunostaining]. EBV infection correlated with sex (39% male v 23% female; P < .001), histologic subtype (69% mixed cellularity v 22% nodular sclerosis v 6% lymphocyte predominance; P < .001) and young age."

Claviez - J Clin Oncol 2005 abstract / PubMed

Epstein-Barr virus is associated with all histological subtypes of Hodgkin lymphoma in Vietnamese children with special emphasis on the entity of lymphocyte predominance subtype. KC Chang, NT Khen, D Jones, IJ Su. Hum Pathol 2005 Jul;36(7):747-755. "In situ hybridization for EBV-encoded RNA revealed that the tumor cells were positive in 93.2% (41/44) of cases, including all 3 cases of nodular lymphocyte predominance HL."

Chang - Hum Pathol 2005 abstract / PubMed
[Association of Hodgkin lymphoma with Epstein-Barr virus in Hungary]. K Keresztes, B Bessenyei, Z Szöllosi, Z Beck, Z Miltényi, Z Nemes, E Oláh, A Illés. Orv Hetil 2005 Jul 24;146(30):1575-1582. "Out of 109 cases, 61 patients (56%) showed virus positivity by PCR while latent membrane protein 1 positivity was found in 47 cases (43%). As regards to gender ratio, 53% female and 58% male patients were virus positive by PCR. Epstein-Barr virus association did not show any alteration in children (1-14 years) when compared to that of adults (out of the 10 children 6 were positive by PCR). As regards to the lifestyle of Epstein-Barr virus positive patients, the incidence of smoking and the ratio of poor social conditions were significantly higher. Mixed cell type was the most frequent (65%) in these patients and Epstein-Barr PCR virus positivity was highest in this type (60%), primarily in age groups 11-20 and over 51 years. Epstein-Barr virus PCR positivity was 52% in nodular sclerosis (negative cases cumulated in the age group 15-30 years), other histologic subtypes could not be evaluated due to the small number of cases."

Keresztes - Orv Hetil 2005 abstract / PubMed

Epstein-Barr virus infection is not the sole cause of high prevalence for Hodgkin's lymphoma in Saudi Arabia. K Al-Kuraya, R Narayanappa, F Al-Dayel, H El-Sohl, A Ezzat, H Ismail, A Belgaumi, P Bavi, V Atizado, G Sauter, R Simon. Leuk Lymphoma 2006 Apr;47(4):707-713. 169 HLs from Saudi Arabia and 30 HLs from Europe. 42/147 (28.6%) and 9/30 (30%) respectively were positive for EBV by ISH.

Al-Kuraya - Leuk Lymphoma 2006 abstract / PubMed

[Prevalence of lymphoma subtypes in Shanxi according to latest WHO classification]. JF Wang, YZ Wang, ZW Chen, RC Taylor. Zhonghua Bing Li Xue Za Zhi 2006 Apr;35(4):218-223. 62/447 lymphoma cases (13.9%) were classic Hodgkin lymphoma; 37 (59.7%) were positive for EBV. "In classic HL, there was complete concordance of results by both EBER in-situ hybridization and LMP-1 immunohistochemistry."

Wang - Zhonghua Bing Li Xue Za Zhi 2006 abstract / PubMed

The effect of Epstein-Barr virus status on clinical outcome in Hodgkin's lymphoma. JM Kwon, YH Park, JH Kang, K Kim, YH Ko, BY Ryoo, SS Lee, SI Lee, HH Koo, WS Kim. Ann Hematol 2006 Jul;85(7):463-468. Results differed by method: In 56 HL patients, "EBV infection was identified in 41.1% of cases by EBER ISH, 26.8% by LMP1 expression, and 26.8% by LMP1 and EBER ISH. EBER-positive HL were significantly more frequent in mixed cellularity (MC) subtype (P=0.014) and advanced stage (P=0.034)."

Kwon - Ann Hematol 2006 abstract / PubMed

The high frequency of EBV infection in pediatric Hodgkin lymphoma is related to the classical type in Bahia, Brazil. I Araujo, AL Bittencourt, HS Barbosa, EM Netto, NM Mendonça, HD Foss, M Hummel, H Stein. Virchows Arch 2006 Sep;449(3):315-319. 90 pediatric HL cases. "EBV-positive tumor cells were found exclusively in cHL. The infection occurred with high frequency in all cHL subtypes, but it predominated in the mixed cellularity and lymphocyte depletion subtypes. These results reinforce the hypothesis that EBV plays a major role in the etiology of pediatric cHL in developing
areas. Curiously, the frequency of EBV infection in HL was identical to the previously described for Burkitt's lymphoma in the same pediatric population. As both lymphomas have a postulated precursor cell in the germinal center (GC), the pattern of latently EBV-infected GC cells previously described in Bahia may be related to the development of these lymphomas.

Araujo - Virchows Arch 2006 abstract / PubMed

Epstein-barr virus and hodgkin lymphoma. RF Ambinder. Hematology Am Soc Hematol Educ Program 2007;2007:204-209. Review. "The association of infectious mononucleosis and HL is strongest in young adults, but virus in tumor cells is least frequently detected in tumors in young adults. This paradox led to concern that there were uncontrolled confounding factors in cohort studies that had been missed, or that the childhood environment characteristics associated with risk of HL in young adults might also be associated with an increased risk of infectious mononucleosis. Alternatively, EBV might be an etiologically innocent passenger, or the virus might be lost from the neoplastic cells during progression (a phenomenon that is readily demonstrated in EBV BL cell lines in vitro but that is largely hypothetical in vivo)."

Ambinder / Hematology 2007 full article

Association of Hodgkin's lymphoma with Epstein Barr virus infection. E Cickusić, J Mustedanagić-Mujanović, E Iljazović, Z Karasalihović, I Skaljić. Bosn J Basic Med Sci 2007 Feb;7(1):58-65. 81 cases of Hodgkin's lymphoma. Results differed by method: "In neoplastic cells, using an immunohistochemical method, latent membrane protein 1 (LMP1) was found in 33,3% of cases, while in situ hybridization results demonstrated the presence of EBER RNA in 48,1% of the cases. EBER RNA was found in non-neoplastic lymphocytes in 38,3% of cases."


Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma. H Hjalgrim, KE Smedby, K Rostgaard, D Molin, S Hamilton-Dutoit, ET Chang, E Ralfkiaer, C Sundström, HO Adami, B Glimelius, M Melbye. Cancer Res 2007 Mar 1;67(5):2382-2388. 586 patients with classic HL and 3,187 controls in Denmark and Sweden. "IM was associated with an increased risk of EBV-positive [OR, 3.23; 95% confidence interval (95% CI) 1.89–5.55] but not EBV-negative HL (OR, 1.35; 95% CI, 0.86–2.14). Risk of EBV-positive HL varied with time since IM and was particularly pronounced in younger adults (OR, 3.96; 95% CI, 2.19–7.18). IM-associated lymphomas occurred with a median of 2.9 years (1.8–4.9 years) after infection. The EBV specificity of the IM association was corroborated by a case-case comparison of IM history between younger adult EBV-positive and EBV-negative HL patients (ORIM EBV+ HL versus EBV− HL, 2.68; 95% CI, 1.40–5.12)."

Hjalgrim / Cancer Res 2007 full article

HLA-A*02 is associated with a reduced risk and HLA-A*01 with an increased risk of developing EBV+ Hodgkin lymphoma. M Niens, RF Jarrett, B Hepkema, IM Nolte, A Diepstra, M Platteel, N Kouprie, CP Delury, A Gallagher, L Visser, S Poppema, GJ te Meerman, A van den Berg. Blood 2007 Nov 1;110(9):3310-3315. 70 patients with
EBV+ HL, 31 patients with EBV- HL, and 59 control participants. "HLA-A*01 was significantly overrepresented and HLA-A*02 was significantly underrepresented in patients with EBV+ HL versus controls and patients with EBV- HL. In addition, HLA-A*02 status was determined by immunohistochemistry or HLA-A*02-specific polymerase chain reaction (PCR) on 152 patients with EBV+ HL and 322 patients with EBV- HL. The percentage of HLA-A*02+ patients in the EBV+ HL group (35.5%) was significantly lower than in 6107 general control participants (53.0%) and the EBV- HL group (50.9%)."

Niens - Blood 2007 abstract / PubMed

Changing patterns in the frequency of Hodgkin lymphoma subtypes and Epstein-Barr virus association in Taiwan. KC Chang, PC Chen, D Jones, IJ Su. Cancer Sci 2008 Feb;99(2):345-349. 99 cases of HL diagnosed between 1996 and 2007, and 74 cases between 1982 and 1995. "The overall EBV positivity rate was 50% (86/173 cases). Comparing the distribution of HL cases diagnosed at two different time periods, we found an increased frequency of the nodular sclerosis (NS) subtype (53 vs 68%, P = 0.045), a decreased frequency of the mixed cellularity subtype (35 vs 13%, P < 0.001), a reduced male-to-female ratio (2.9:1 compared to 1.4:1) and mean age (42.4 vs 36.6 years) in the NS subtype, and a significant decrease in EBV positivity rates among the NS and lymphocyte-depletion subtypes (61 vs 39%, P = 0.03). These data indicate shifts in the frequency of histological subtype and EBV association for HL in Taiwan over the last decade, with a trend closer to that seen in Western countries and Japan."

Chang - Cancer Sci 2008 abstract / PubMed

Analysis of Epstein-Barr virus strains and variants in classical Hodgkin's lymphoma by laser microdissection. M García-Cosío, A Santón, P Martín, ME Reguero, E Cristóbal, C Bellas. Histol Histopathol 2008 Feb;23(2):209-217. In 10 HIV-positive and 16 sporadic cHL cases, EBV EBERs were present in all but 2 sporadic cHL cases.

García-Cosío - Histol Histopathol 2008 abstract / PubMed

Pediatric Hodgkin lymphoma in 2 South American series: a distinctive epidemiologic pattern and lack of association of Epstein-Barr virus with clinical outcome. PA Chabay, MH Barros, R Hassan, E De Matteo, G Rey, MK Carrico, IZ Renault, MV Preciado. J Pediatr Hematol Oncol 2008 Apr;30(4):285-291. EBV expression was detected in 52% of cases (54% in Argentina and 48% in Brazil). "In Arg HL, EBV positivity was significantly higher in patients<or=10 years (P=0.0011)."

Chabay - J Pediatr Hematol Oncol 2008 abstract / PubMed

Expression of Epstein-Barr virus in Hodgkin lymphoma in a population of United Arab Emirates nationals. S Al-Salam, A John, S Daoud, SM Chong, A Castella. Leuk Lymphoma 2008 Sep;49(9):1769-77. "Nodular sclerosis (NS) subtype was the most common type of HL among UAE nationals followed by mixed cellularity (MC), lymphocytic predominant (LP), unclassified, lymphocytic depletion (LD) and lymphocyte rich (LR) subtypes, respectively. EBV was seen in 17 of 45 (38%) cases of HL and was predominately seen in the MC subtype followed by NS, LD and LR subtypes, respectively. EBV was more frequently expressed in HL in the pediatric age group than the adult age group."


Latent Epstein-Barr Virus Infection of Tumor Cells in Classical Hodgkin's Lymphoma Predicts Adverse Outcome in Older Adult Patients. A Diepstra, GW van Imhoff, M Schaalveld, H Karim-Kos, A van den Berg, E Vellenga, S Poppema. J Clin Oncol 2009 Aug 10;27(23):3815-21. 34% of 412 patients were positive for EBV in tumor cells.

Plasma EBV-DNA monitoring in Epstein-Barr virus-positive Hodgkin lymphoma patients. M Spacek, P Hubacek, J Markova, M Zajac, Z Vernerova, K Kamaradova, J Stuchly, T Kozak. APMIS 2011 Jan;119(1):10-16. 29 of 150 patients were EBV-positive by ISH for EBER, or by IHC for LMP1. "EBV-positive HL was significantly associated with EBV-DNA positivity both in the plasma and whole blood in pretreatment samples, increasing age and MC subtype. Serial analysis of plasma EBV-DNA showed that response to therapy was associated with decline in viral load. Moreover, significantly increased plasma EBV-DNA level recurred before disease relapse in one patient."

Disease patterns in pediatric classical Hodgkin lymphoma: a report from a developing area in Brazil. MH Barros, R Hassan, G Niedobitek. Hematol Oncol 2011 Mar 4 doi: 10.1002/hon.984 [Epub ahead of print]. 100 consecutive cases. "EBV was identified in 44.8% of cases, without preferential association with age groups (≤10 years vs. >10 years). [Mixed cellularity] cases were independently associated with EBV infection of tumour cells (p = 0.045) and with a CD4/CD20 ratio <1 in the microenvironment (p = 0.014)."
Aberrant Cytoplasmic Expression of Cyclin B1 Protein and its Correlation with EBV-LMP1, P53 and P16(INK4A) in Classical Hodgkin Lymphoma in China. P Zhao, Y Lu, L Liu, M Zhong, Pathol Oncol Res 2011 Jun;17(2):369-373. EBV-LMP1 was overexpressed in 85% of Hodgkin lymphomas. "Cyclin B1 was positively correlated with EBV-LMP1 (P < 0.001) and P53 (P < 0.001), but was inversely related to P16(INK4A) (P < 0.05)."

Example: Anti-smoking junk

Cigarette smoking and risk of Hodgkin's Disease: A population-based case-control study. NC Briggs, HI Hall, EA Brann, CJ Moriarty, RS Levine. Am J Epidemiol 2002;156(11):1011-1020. "Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals adjusted for age, registry, race/ethnicity, Jewish upbringing, education, and childhood domicile. Compared with never smokers, current smokers had a significantly increased risk of Hodgkin’s disease (odds ratio (OR) = 1.8, 95% confidence interval (CI): 1.3, 2.9)." They simply ignored EBV infection! This is an example of deliberate anti-smoker scientific fraud, under the auspices of the Centers for Disease Control, and published by the corrupt Johns Hopkins Bloomberg School of Public Health. In the year 2002, when no one can legitimately pretend ignorance, they purposely ignore the role of EBV infection, in order to falsely blame by confounding.

Cigarette smoking and risk of Hodgkin lymphoma: a population-based case-control study. H Hjalgrim, K Ekström-Smedby, K Rostgaard, RM Amini, D Molin, S Hamilton-Dutoit, C Schöllkopf, ET Chang, E Ralfkiaer, HO Adami, B Glimelius, M Melbye. Cancer Epidemiol Biomarkers Prev 2007 Aug;16(8):1561-1566. 586 classic HL cases and 3,187 population controls in a Danish-Swedish case-control study. "Odds ratios (OR) for an association with cigarette smoking were calculated by logistic regression for HL overall and stratified by age, sex, major histology subtypes, and tumor EBV status, adjusting for known confounders. RESULTS: Compared with never smokers, current cigarette smokers were at an increased overall HL risk [adjusted OR, 1.57; 95% confidence interval (95% CI), 1.22-2.03]. The association was strongest for EBV-positive HL (adjusted OR, 2.36; 95% CI, 1.51-3.71), but also applied to EBV-negative HL (adjusted OR, 1.43; 95% CI, 1.05-1.97; P(homogeneity EBV-pos) versus P(homogeneity EBV-neg) = 0.04). The association did not vary appreciably by age, sex, or histologic subtype, the apparent EBV-related difference present in all strata. There was no evidence of a dose-response pattern, whether by age at smoking initiation, daily cigarette consumption, number of years smoking, or cumulative number of cigarettes smoked." [The known confounder they ignored is that EBV infection occurs earlier as well as more frequently in the lower socioeconomic classes, of which smokers are more likely to belong.]
The National Cancer Institute claims that "At this time, the cause or causes of Hodgkin's disease are not known," and insists on calling EBV merely a "risk factor:" "Viruses -- Epstein-Barr virus is an infectious agent that may be associated with an increased chance of getting Hodgkin's disease." They refuse to admit that EBV is CAUSAL, and not merely associated with an increased chance of getting Hodgkin disease. (Risk Factors Associated with Hodgkin's Disease. National Cancer Institute. Posted 06/25/1999, Updated 09/16/2002; viewed 11-30-02, 06-18-05, 10-02-05, and 07-01-06.)

See the American Cancer Society drag its feet about EBV and HD!

The American Cancer Society mirrors the attitude of the NCI in its evasion of the causal role of EBV. "There seems to be a slightly increased rate for Hodgkin's disease in people who have had infectious mononucleosis (sometimes called "mono" for short), an infection caused by the Epstein-Barr virus. However, half of patients with Hodgkin's disease show no evidence of a previous Epstein-Barr virus infection." And they insist that "Even if someone has one or more risk factors for Hodgkin's disease, it is impossible to know for sure how much that risk factor could contribute to causing the cancer. In general, we can say that no major risk factors for Hodgkin's disease have been discovered yet." (What Are the Risk Factors for Hodgkin's Disease? American Cancer Society, as of 10-02-05 and 07-01-06.)

**EBV and Burkitt lymphoma**

Precipitating antibody in human serum to an antigen present in cultured Burkitt's lymphoma cells. LJ Old, EA Boyse, HF Oettgen, ED Harven, G Geering, B Williamson, P Clifford. Proc Natl Acad Sci U S A 1966 Dec;56(6):1699-1704. 19 of 20 (95%) sera of patients with carcinoma of the postnasal space were positive to an antigen prepared from cultured Burkitt's lymphoma cells.

Old - PNAS 1966 full article / PubMed

A Burkitt lymphoma cell line with integrated Epstein-Barr virus at a stable chromosome modification site. NC Popescu, MC Chen, S Simpson, S Solinas, JA DiPaolo. Virology 1993 Jul;195(1):248-251. "Virus insertion into chromosomal DNA caused a stable modification site expressed as a distinctive achromatic region adjacent to the band 2p13. The chromatid lesion at the site of EBV integration involving a recombinogenic and fragile site may have contributed to the development of the NAB-2 BL."

Popescu - Virology 1993 abstract / PubMed

The role of Epstein-Barr virus-encoded small RNAs (EBERs) in oncogenesis. A Nanbo, K Takada. Rev Med Virol 2002 Sep-Oct;12(5):321-326. "EBERs play a key role in the maintenance of malignant phenotypes of Burkitt's lymphoma (BL) cells... Furthermore, we demonstrated that EBERs confer resistance to interferon (IFN)-alpha-induced apoptosis by inhibition of double-stranded (ds) RNA-activated protein kinase (PKR).
which is the key mediator of the antiviral effect of IFN-alpha. These studies provide a new notion that RNA molecules contribute to oncogenesis."


Frequent presence of subtype A virus in Epstein-Barr virus-associated malignancies. SC Peh, LH Kim, S Poppema. Pathology 2002 Oct;34(5):446-450. In 17 Hodgkin's, 14 Burkitt's, 4 T-cell and 3 B-cell non-Hodgkin's lymphomas, "All cases showed presence of type A virus, consistently detected with nested PCR protocol but not with single step PCR. There was no type B virus or mix infections detected."

Peh - Pathology 2002 abstract / PubMed


Kelly / Hematology Am Soc Hematol Educ Program 2007 full article


Brady / J Clin Pathol 2007 full article

Sporadic paediatric and adult Burkitt lymphomas share similar phenotypic and genotypic features. SS Chuang, WT Huang, PP Hsieh, YC Jung, H Ye, MQ Du, CL Lu, CY Cho, SC Hsiao, YH Hsu, KJ Lin. Histopathology 2008 Mar;52(4):427-435. In 17 paediatric and 14 adult BLs, 24% versus 21% were positive for EBER.

Chuang - Histopathology 2008 abstract / PubMed

Detection of Epstein-Barr virus in children and adolescents with Burkitt's lymphoma by in situ hybridization using tissue microarrays. M Pizza, P Bruniera, SM Luporini, HR Marcelino da Silva, ML Borsato, HC de Castro, FA Soares, RA Paes. Hematology 2008 Apr;13(2):114-118. "The presence of EBV using in situ hybridization was found in 33/50 (66%) and there was no association between the presence of the virus in the tumor cells or patient age, as well as the survival rate."

Pizza - Hematology 2008 abstract / PubMed

Viral Studies in Burkitt Lymphoma: Association With Epstein-Barr Virus but Not HHV-8. EM Queiroga, G Gualco, L Chioato, WJ Harrington, I Araujo, LM Weiss, CE Bacchi. Am J Clin Pathol 2008 Aug;130(2):186-192. "EBV was present in 45.0% of all BL cases with higher incidence in the pediatric group; most cases were EBV type A. We found no association of BL with HHV-8 in EBV + BL or in EBV-cases, including the HIV + BL group." Number of cases is not given in the abstract.

Queiroga - Am J Clin Pathol 2008 abstract / PubMed
Burkitt lymphoma in Brazil is characterized by geographically distinct clinicopathologic features. EM Queiroga, G Gualco, LM Weiss, DP Dittmer, I Araujo, CE Klumb, WJ Harrington Jr, CE Bacchi. Am J Clin Pathol 2008 Dec;130(6):946-956. "234 patients from 5 geographic regions that are widely disparate socioeconomically, including pediatric (61.1%) and adult (37.6%) populations. EBV was present in 52.6% of all BL cases, varying from 29% (12/42) in the South to 76% (13/17) in the North. Most of the cases were EBV type A. The frequency was higher in the pediatric group, and EBV association within this age range predominated in all regions except the South."

Queiroga - Am J Clin Pathol 2008 abstract / PubMed

Children with endemic Burkitt lymphoma are deficient in EBNA1-specific IFN-gamma T cell responses. AM Moormann, KN Heller, K Chelimo, P Embury, R Ploutz-Snyder, JA Otieno, M Oduor, C Münz, R Rochford. Int J Cancer 2009 Apr 1;124(7):1721-1726. "Significantly fewer children with eBL, 16% (7/44) had EBNA1-specific IFN-gamma responses in contrast to healthy children living in a malaria holoendemic area or in an area with sporadic malaria transmission, 67% (40/60) and 72% (43/60) responders, respectively (p < 0.003). Children with eBL maintained IgG(1) dominated antibody responses to EBNA1 similar to healthy children suggesting a selective loss of IFN-gamma secreting EBNA1-specific T cells in the presence of intact humoral immunity. CD8(+) T cell responses to EBV lytic and latent antigens not expressed in the tumors were similarly robust in eBL patients compared to healthy children. In addition, CD4(+) T cell responses to a malaria protein, merozoite surface protein 1, were present in lymphoma patients."

Moormann - Int J Cancer 2009 abstract / PubMed

EBV & Other Lymphomas


Sauerbrei - Arch Geschwulstforsch 1987 abstract / PubMed


Su - Cancer 1990 abstract / PubMed

Frequent latent Epstein-Barr virus infection of neoplastic T cells and bystander B cells in human immunodeficiency virus-negative European peripheral pleomorphic T-cell lymphomas. P Korbjahn, I Anagnostopoulos, M Hummel, M Tiemann, F Dallenbach, MR Parwaresch, H Stein. Blood 1993 Jul 1;82(1):217-223. 38 of 81 cases (47%) of PMTCL were positive for EBER by ISH. "By EBER-ISH, the virus was located in the tumor cells in 30 of the 38 EBV-positive cases, with the proportion of the infected cells ranging from 1% to 100%. In 18 of these cases and in the 8 cases without EBV-infected
tumor cells, the virus was, respectively, either additionally or exclusively detectable in occasional nonmalignant lymphoid bystander cells."

Korbjuhn - Blood 1993 full article (pdf, 7pp)

Sinonasal T-cell lymphoma in the differential diagnosis of lethal midline granuloma using in situ hybridization for Epstein-Barr virus RNA. M Dictor, A Cervin, O Kalm, E Rambech. Mod Pathol 1996 Jan;9(1):7-14. 12 cases of primary sinonasal T-cell lymphoma, 23 cases of nonspecific rhinitis and 10 cases of Wegener's granulomatosis. "All hybridizable lymphoma sections, regardless of phase of development, gave a strong ISH signal easily detected at low magnification in 50 to 100% of tumor cells. Scattered positive cells were usually present even in necrotic areas. In contrast, no case of Wegener's granulomatosis or nonspecific rhinitis produced a true hybridization signal."

Dictor - Mod Pathol 1996 abstract / PubMed


Tamura - Nippon Jibiinkoka Gakkai Kaiho 1996 abstract / PubMed


Kanavaros - Leukemia 1996 abstract / PubMed

[Epstein-Barr virus infection in midline malignant reticulosis]. W Liu, J van Gorp, G Li. Zhonghua Zhong, Liu, Za Zhi 1997 Jan;19(1):49-52. "ALCs [atypical lymphoid cells] were positive for EBER 1/2 in 31/37 (83.8%) cases; EBV-DNA was detected in 12/15 (77.8%) cases; LMP was expressed in some ALCs in 5/19 (26.3%) cases."


Kawa - Nippon Rinsho 1997 abstract / PubMed

Natural killer cell lymphoma/leukemia: pathology and treatment. YL Kwong, AC Chan, RH Liang. Hematol Oncol 1997 May;15(2):71-79. Review. "A consistent association with monoclonal Epstein-Barr virus infection in the tumour cell has been observed... Clinically, most cases occur in the nasal area and upper aerodigestive tract. However, occurrence in non-nasal sites such as the skin, gastrointestinal tract and testis is also observed."

Kwong - Hematol Oncol 1997 abstract / PubMed
Nonnasal lymphoma expressing the natural killer cell marker CD56: A clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. KC John, VC Sin, KF Wong, CS Ng, WYW Tsang, CH Chan, MMC Cheung, WH Lau. Blood 1997 Jun 15;89(12):4501-4513. 32/34 (94%) of nasal-type NK/T cell lymphomas were EBV-positive. 5/5 (100%) of NK cell leukemia/lymphomas were EBV-positive. One case each of hepatosplenic T-cell lymphoma and S100 protein+ T-cell lymphoproliferative disease and two cases each of T-chronic lymphocytic/prolymphocytic leukemia, lymphoblastic lymphoma, and true histiocytic lymphoma were EBV-negative.

John / Blood 1997 full article


Lee - Int J Dermatol 1997 abstract / PubMed

Integrated and episomal forms of Epstein-Barr virus (EBV) in EBV associated disease. K Oshima, J Suzumiya, M Kanda, M Kikuchi. Cancer Lett 1998 Jan 9;122(1-2):43-50. "Integrated EBV was demonstrated in 11 of 104 cases; five of 14 cases with B cell lymphoma (36%), one of 12 cases with nasopharyngeal carcinomas (8%), four of 31 cases with natural killer (NK) leukemia/lymphoma (13%) and one of 11 cases with chronic EBV infection (9%). However, none of the 24 T cell lymphoma, seven Hodgkin's disease, or five acute EBV infection cases showed integrated EBV. In addition, seven of the 11 cases with EBV integration (five B cell lymphoma and two NK leukemia/lymphoma) showed only an integration form, however, the other four (two NK leukemia/lymphoma, one nasopharyngeal carcinoma and one chronic EBV infection) showed both integrated and episomal forms. The integrated form was frequently found in B cell lymphoma and especially in high grade B cell lymphoma."

Ohshima - Cancer Lett 1998 abstract / PubMed

lymphomatoid granulomatosis type) were Epstein-Barr virus (EBV)-positive." 13/14 nasal-type natural killer (NK)/T-cell lymphomas were EBV-positive.


Epstein-Barr virus (EBV)-infected cells were frequently but dispersely detected in T-cell lymphomas of various types by in situ hybridization with an RNA probe specific to EBV-specific nuclear antigen 1. T Yamamoto, Y Nakamura, K Kishimoto, H Takeuchi, M Shirakata, T Mitsuya, K Hirai. Virus Res 1999 Dec 1;65(1):43-55. "Using ISH with improved antisense RNA probe specific to EBNA-1 mRNA, the virus was detected in 19 (59%) of 32 cases, whereas the EBER1 transcript was found in only 15 (47%) of 32 cases by conventional EBER-ISH, resulting in 21 EBV-positive cases (66%) by combining the two methods."

Yamamoto - Virus Res 1999 abstract / PubMed


Akashi - Leuk Lymphoma 2000 abstract / PubMed


Koch - Laryngorhinootologie 2001 abstract / PubMed

Diagnostic and prognostic implications of circulating cell-free Epstein-Barr virus DNA in natural killer/T cell lymphoma. KI Lei, LY Chan, WY Chan, PJ Johnson, YM Lo. Clin Cancer Res 2002 Jan;8(1):29-34. "Plasma EBV DNA, as measured by real-time quantitative PCR, is a useful tumor marker for diagnosis, disease monitoring, and prediction of outcome in patients with NK/T cell lymphoma."

Lei - Clin Cancer Res 2002 abstract / PubMed
Lei - Clin Cancer Res 2002 Full Article

Epstein-barr virus-associated non-Hodgkin's lymphoma of B-cell origin, Hodgkin's disease, acute leukemia, and systemic lupus erythematosus: a serologic and molecular analysis. W Mitarnun, J Pradutkanchana, S Takao, V Saechan, S Suwiwat, T Ishida. J Med Assoc Thai 2002 May;85(5):552-9. In 58 patients, "EBV internal repeat-1 region (IR-1) in peripheral blood CD3+ cells was detected in 10 of 14 patients (71.5%) with NHL-B, 3 of 8 patients (37.5%) with Hodgkin's disease, 1 of 6 patients (16.7%) with
acute leukemia, 4 of 9 patients (44.5%) with SLE, and was not detected in any of the 21 patients with other diseases."

**Mitarnun 2002 J Med Assoc Thai abstract / PubMed**


**Zhang / Chin Med J (Engl) 2003 full article**

Epstein-Barr virus in biopsies from patients with Hodgkin and non-Hodgkin lymphoma at the University of Puerto Rico immunohistochemistry laboratory. FJ Córdova Pérez, CI González-Keelan, R Vélez. P R Health Sci J 2003 Jun;22(2):125-129. "We found an LMP-1 positive rate of 50% for 22 cases of HL and 35% for 63 cases of NHL. Among HL, 5 were children and 16 were adults, with LMP-1 positive rates of 60% and 50% respectively. Among NHL, 3 were children and 59 were adults, with equal LMP-1 positive rates of 33%."  

**Córdova Pérez - P R Health Sci J 2003 abstract / PubMed**

Prevalence and characterization of anaplastic large cell lymphoma and its association with Epstein-Barr virus in Pakistani patients. S Noorali, S Pervez, N Yaqoob, T Moatter, MI Nasir, S Haroon, E Hodges, JL Smith. Pathol Res Pract 2004;200(10):669-679. "Association of Epstein-Barr virus (EBV) was noted in seven out of 28 cases (25%) of ALCL by PCR, whereas ISH for EBV-encoded nuclear RNA-1 (EBER-1) detected the presence of EBV in two (16.7%) out of 12 cases, where one was T-cell ALCL and the other null-cell ALCL. Immunostaining for LMP-1 could not be performed, because tissue material was not available."

**Noorali - Pathol Res Pract 2004 abstract / PubMed**


**Kuo - Int J Surg Pathol 2004 abstract / PubMed**

Features of intestinal T-cell lymphomas in Chinese population without evidence of celiac disease and their close association with Epstein-Barr virus infection. WY Zhang, GD Li, WP Liu, Q Ouyang, XC Ren, FY Li, H Xu. Chin Med J (Engl) 2005 Sep 20;118(18):1542-1548. "EBER1/2 was detected in 41 (97.6%) of the 42 patients. The expression frequency of LMP-1 was 38.1% (16/42)."

**Zhang - Chin Med J (Engl) 2005 abstract / PubMed**
Epstein-Barr viral infection in extranodal lymphoma of the head and neck: correlation with prognosis and response to treatment. AA Bahnassy, AR Zekri, N Asaad, S El-Houssini, HM Khalid, LM Sedky, NM Mokhtar. Histopathology 2006 Apr;48(5):516-528. "The study included 50 PELHN (11 cases in the nose and paranasal sinuses, 11 in the nasopharynx, 13 in the tonsils, seven in the oropharynx and eight in the oral cavity), five reactive lymph nodes, 15 normal nasopharyngeal tissue and 25 throat washes of healthy subjects from Egypt.... EBV was detected in 90% and 70% of the cases using EBER in situ hybridization and PCR, respectively. All cases of nasal type lymphoma were positive for EBV."

Bahnassy - Histopathology 2006 abstract / PubMed

[Prevalence of lymphoma subtypes in Shanxi according to latest WHO classification]. JF Wang, YZ Wang, ZW Chen, RC Taylor. Zhonghua Bing Li Xue Za Zhi 2006 Apr;35(4):218-223. 385/447 (86.1%) lymphoma cases were non-Hodgkin lymphoma (NHL). "Of the NHL cases, 68.3% were of B-cell lineage and 30.6% were of T and/or NK-cell lineage. Histiocytic neoplasm accounted for only 0.8% (3 cases). As for the subtyping of NHL, diffuse large B-cell lymphoma was commonest (35.1%), followed by peripheral T-cell lymphoma, NOS (12.0%), extranodal marginal zone B-cell lymphoma (MALT lymphoma) (11.7%), follicular lymphoma (8.6%), T-lymphoblastic lymphoma (7.0%), anaplastic large cell lymphoma (4.2%), B-small lymphocytic lymphoma (3.6%) and mantle cell lymphoma (2.6%).... Regarding markers for EB virus infection, 14 cases of the B-cell lymphoma gave positive findings with both EBER in-situ hybridization and LMP-1 immunohistochemistry, while 6 of the T/NK-cell lymphoma expressed LMP-1 and 19 showed positive signals for EBER. In NHL, there was discordance in EBER in-situ hybridization and LMP-1 immunohistochemical results."

Wang - Zhonghua Bing Li Xue Za Zhi 2006 abstract / PubMed

Tissue markers of Epstein-Bar virus (EBV) infection in B-cell non-Hodgkin's lymphomas. A Kasprzak, R Spachacz, A Halon, M Jelen, K Stefanska, J Wachowiak, E Trejster, M Zabel. Med Wieku Rozwoj 2006 Jul-Sep;10(3 Pt 1):639-648. Archive tissue material from 26 children and from 27 adults with B-cell NHLs, using immunocytochemical techniques, in situ hybridisation, and PCR. "The detectability and expression of EBV infection were significantly higher in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients. Expression of EBNA2 and LMP1 and that of EBERs in B-cell NHLs involved mainly cells of CD20(+) phenotype. Positive correlation was confirmed between expression of EBNA2 and LMP1 as well as between expression of the two proteins and EBERs in children with B-cell NHLs as compared to adult patients.

Kasprzak - Med Wieku Rozwoj 2006 abstract / PubMed

[Expression of ZEBRA protein of Epstein-Barr virus in Hungarian patients with Hodgkin lymphoma: latent or lytic cycle?] Z Beck, A Illés, K Keresztes, B Bessenyei, Z Szöllös, A Kis, E Oláh. Orv Hetil 2006 Aug 20;147(33):1539-1544. 47/109 [43.1%] HL and 18/59 [30.5%] NHL samples were positive for LMP1.
Beck - Orv Hetil 2006 abstract / PubMed

[Nasal and pharyngeal non-Hodgkin lymphomas and their relationship with Epstein-Barr virus: a report of 158 cases]. YJ He, XS Jia, K Hasui, EH Wang, AG He. Zhonghua Bing Li Xue Za Zhi 2007 Feb;36(2):94-97. "Among 99 cases studied by EBER-1 in situ hybridization, a positive detection was seen in 70/71 cases (98.6%) of extranodal NK/T cell lymphoma (nasal type), 8/12 cases (66.7%) of T cell lymphoma, and 7/16 cases (43.8%) of B cell lymphoma."

He - Zhonghua Bing Li Xue Za Zhi 2007 abstract / PubMed

Nasal natural killer/T-cell lymphoma and its association with type "i"/XhoI loss strain Epstein-Barr virus in Chile. ME Cabrera, Y Eizuru, T Itoh, C Koriyama, Y Tashiro, S Ding, S Rey, S Akiba, A Corvalan. J Clin Pathol 2007 Jun;60(6):656-660. 7 out of 9 (78%) of WHO-criteria nasal NK/T-cell lymphomas were positive for EBV.

Cabrera - J Clin Pathol 2007 abstract / PubMed

Expression of the Epstein-Barr virus in lymphoproliferative diseases of the lung. M Shimakage, H Sakamoto, S Harada, T Sasagawa, K Kodama. Oncol Rep 2007 Jun;17(6):1347-1352. "Two non-Hodgkin's lymphomas (NHL) originating in the lung, 5 mucosal-associated lymphoid tissue lymphomas (MALT lymphoma) of the lung, 1 lymphoid hyperplasia of the lung and 1 lymphoid interstitial pneumonia (LIP), were subjected to mRNA in situ hybridization, indirect immunofluorescence staining and PCR. mRNA in situ hybridization using BamHI, BamHIY1Y2, the Epstein-Barr virus nuclear antigen (EBNA) and the EBV encoded small non-polyadenylated RNA (EBER1) probe revealed signals in all the examined samples, although some samples showed weak signals by using the EBER1 probe. Indirect immunofluorescence staining using the anti-leader protein, anti-EBNA2, the anti-latent member protein-1 and anti-BamHIZ coding leftward reading frame-1 antibodies showed definitive fluorescence. PCR also revealed EBV DNA in these specimens. EBV infected all the lymphoproliferative diseases of the lung irrespective of the histological or clinical stages. Furthermore, EBV infected not only the atypical lymphocytes but also the macrophages in the tissues of these diseases."

Shimakage - Oncol Rep 2007 abstract / PubMed
Shimakage / Oncol Rep 2007 full article (pdf, 6 pp)

EBV viral load in tumor tissue is an important prognostic indicator for nasal NK/T-cell lymphoma. PP Hsieh, CL Tung, AB Chan, JB Liao, JS Wang, HH Tseng, HH Su, KC Chang, CC Chang. Am J Clin Pathol 2007 Oct;128(4):579-584. 19 cases. "Patients with a low EBV viral load (<1 copy per cell) more frequently survived for more than 2 years compared with patients with a high EBV viral load (>1 copies/cell) (7/7 vs 3/9; P = .014; Fisher exact test). Furthermore, the patients with low EBV viral loads had a better overall survival than patients with high viral loads (50% accumulative survival: not reached vs 4-5 months; Kaplan-Meier survival analysis; P = .049). In contrast, the overall survival of the patients did not correlate with the extent of lesion, age, stage, necrosis, histologic subtypes, CD56 expression, or angiocentric or angiodestructive growth pattern."
Epstein-Barr virus infection and risk of lymphoma: immunoblot analysis of antibody responses against EBV-related proteins in a large series of lymphoma subjects and matched controls. S de Sanjosé, R Bosch, T Schouten, S Verkuijlen, A Nieters, L Foretova, M Maynadié, PL Cocco, A Staines, N Becker, P Brennan, Y Benavente, P Boffetta, CJ Meijer, JM Middeldorp. Int J Cancer 2007 Oct 15;121(8):1806-1812. 1,085 incident lymphoma cases from Spain, France, Germany, Czech Republic, Italy and 1,153 age, sex and country matched controls. An abnormal reactive pattern to EBV was observed in 20.9% of 2,238 included subjects with an increased proportion of cases presenting ab_EBV as compared to the control population (23.9% vs. 18.0% p = 0.001). Ab_EBV positivity was a risk factor for all lymphomas combined (odds ratio [OR] = 1.42, 95% confidence interval [CI]=1.15-1.74), and specifically for chronic lymphocytic leukaemia (OR = 2.96, 95%CI = 2.22-3.95).

Correlation of immunophenotype of sinonasal non-Hodgkin's lymphoma to Epstein-Barr virus infection. YF Feng, QL Wu, YS Zong. Ai Zheng 2007 Nov;26(11):1170-1176. "Seventy-one sinonasal NHLs were found in all 1 412 NHLs (71/1 412, 5.03%). Only 57 out of the 71 NHL biopsy tissues were suitable for this study. The median age of the patients was 50 years (ranged from 3 to 75 years). There were 38 males and 19 females. Forty-four sinonasal NHLs (44/57, 77.19%) were NK/T-cell lymphoma, nasal type, all of which were infected with EBV."

Quantitative analysis of cell-free Epstein-Barr virus DNA in the plasma of patients with peripheral T-cell and NK-cell lymphomas and peripheral T-cell proliferative diseases. S Suwiwat, J Pradutkanchana, T Ishida, W Mitarnun. J Clin Virol 2007 Dec;40(4):277-283. Cell-free EBV DNA was detected in 32/38 (84%) of peripheral T-cell and NK-cell lymphoma patients and 5/7 (71%) of peripheral T-cell proliferative disease patients, but not in the 45 controls.


Epstein-Barr virus infection and childhood lymphoma] ZD Xie, L Wang, D Lu, CJ Zhou, KL Shen. Zhonghua Zhong Liu Za Zhi 2008 May;30(5):365-367. IHC and ISH detection of EBV-EBERs in paraffin-embedded specimens of lymphoma collected between 1996 and 2005, including 36 Hodgkin lymphomas (HL) and 51 non-Hodgkin lymphomas (NHL). "EBV was detected in 72.2% (26/36) of the
Hodgkin lymphomas, 15.7% (8/51) of the non-Hodgkin lymphomas and 33.3% (15/45) of the reactive hyperplasia of lymph nodes."

Xie - Zhonghua Zhong Liu Za Zhi 2008 abstract / PubMed

Intravascular large T-cell or NK-cell lymphoma: a rare variant of intravascular large cell lymphoma with frequent cytotoxic phenotype and association with Epstein-Barr virus infection. L Cerroni, C Massone, H Kutzner, T Mentzel, P Umbert, H Kerl. Am J Surg Pathol 2008 Jun;32(6):891-898. 2/4 cases were positive for EBV by ISH, one was negative.


Age-related Epstein-Barr virus-associated B-cell lymphoproliferative disorders: special references to lymphomas surrounding this newly recognized clinicopathologic disease. Y Shimoyama, K Yamamoto, N Asano, T Oyama, T Kinoshita, S Nakamura. Cancer Sci 2008 Jun;99(6):1085-1091. "This new disease entity is characterized pathologically by centroblasts, immunoblasts, and Hodgkin and Reed-Sternberg-like giant cells with a varying degree of reactive components, often posing therapeutic and diagnostic problems for hematologists and pathologists, respectively. The aim of the present review is to briefly summarize the overall clinicopathological profile of this newly recognized age-related (also called 'senile') EBV(+) B-LPD and EBV(+) Hodgkin lymphoma for a practical diagnostic approach."

Shimoyama - Cancer Sci 2008 abstract / PubMed

Histological characteristics of 21 Papua New Guinean children with high-grade B-cell lymphoma, which is frequently associated with EBV infection. Y Nomura, EK Lavu, K Muta, D Niino, M Takeshita, S Hirose, S Nakamura, T Yoshino, M Kikuchi, K Ohshima. Pathol Int 2008 Nov;58(11):695-700. "10 of 12 patients (83%) with BL/BLL, one of four (25%) with DLBCL, and three of five (60%) with B-LBL were positive for EBV-ISH. The findings of EBV-positive B-LBL were surprising because it is commonly considered that lymphoblastic lymphoma is not associated with EBV. EBV positivity was not detected in the 12 Japanese patients who were available for the EBV-ISH evaluation. It is concluded that it is possible that a proportion of DLBCL and B-LBL besides BL/BLL are associated with EBV in endemic region."

Nomura - Pathol Int 2008 abstract / PubMed

Lymphocyte-depleted classic Hodgkin lymphoma-a neglected entity? D Benharroch, A Levy, J Gopas, M Sacks. Virchows Arch 2008 Dec;453(6):611-616. "Changes in the definition of lymphocyte-depleted classic Hodgkin lymphoma (LDCHL) have recently led to reclassification of many cases as other pleomorphic lymphomas.... Twelve of 201 cHL patients (5.9%) were diagnosed as showing LDCHL histology, a higher percentage of LDCHL than in most recent series. The LD cases were most often positive for Epstein-Barr virus and for sialyl-CD15."

Benharroch - Virchows Arch 2008 abstract / PubMed
Low frequency of Epstein Barr virus association and high frequency of p53 overexpression in an Argentinian pediatric T-cell lymphoma series. PA Chabay, E De Matteo, M Lorenzetti, A Vijnovich Barón, P Valva, MV Preciado. Pediatr Dev Pathol 2009 Jan-Feb;12(1):28-34. EBV expression was found in 8.0% of 17 cases.

Chabay - Pediatr Dev Pathol 2008 abstract / PubMed

A prospective study of mitochondrial DNA copy number and risk of non-Hodgkin lymphoma. Q Lan, U Lim, CS Liu, SJ Weinstein, S Chanock, MR Bonner, J Virtamo, D Albanes, N Rothman. Blood 2008 Nov 15;112(10):4247-4249. "Mitochondrial DNA (mtDNA) copy number is increased in patients with chronic lymphocytic leukemia (CLL), in Burkitt lymphoma and Epstein-Barr virus-transformed lymphoblastoid cell lines, and in T cells activated via the T-cell receptor... There was a dose-response relationship between tertiles of mtDNA copy number and risk of NHL..." All subjects were recruited as smokers. "The mtDNA copy number was significantly higher in cases compared with controls (Table 1, P = .013), and the risk for developing NHL increased significantly with increasing mtDNA copy number (Table 2, Ptrend = .046). The association was most pronounced for CLL/SLL [small lymphocytic lymphoma], the most common histologic subtype in this case series (33%), with OR equal to 14.1 (95% CI, 1.9-103.2) for subjects in the highest tertile of mtDNA copy number compared with the lowest tertile."

Lan - Blood 2008 full article / PubMed Central

Frequency and distribution of Epstein-Barr virus infection and its association with P53 expression in a series of primary nodal non-Hodgkin lymphoma patients from South India. PS Sasikala, K Nirmala, S Sundersingh, U Mahji, T Rajkumar. Int J Lab Hematol 2010 Feb;32(1 Pt 2):56-64. "EBV, predominantly type A strain, was detected in 27/87 (31%) nodal lymphoid malignancies, 11/46 diffuse large B-cell lymphomas, 6/17 follicular lymphoma, 4/6 anaplastic large cell lymphomas (ALCL), 5/11 peripheral T-cell lymphomas (PTCL) and 1/7 lymphoblastic lymphomas."

Sasikala - Int J Lab Hematol 2008 abstract / PubMed

The prevalence of Epstein-Barr virus infection in different types and sites of lymphomas. Y Zhang, J Peng, Y Tang, J He, J Peng, Q Zhao, R He, X Xie, X Peng, R Gan. Jpn J Infect Dis 2010 Mar;63(2):132-135. By ISH, "Fifty-six out of 108 non-Hodgkin lymphoma (NHL) cases were positive for EBER (42.6%). The EBER-positivity rate of NHL in the nasal cavity and nasopharynx (35/60 cases, 58.3%) was higher than that of NHL in stomach (9/30 cases, 30%) and in the superficial lymph nodes (2/18 cases, 11.1%) (P<0.05). The EBER-positivity rate of Hodgkin lymphoma in the superficial lymph nodes was 26.3% (5/19 cases)."

Zhang / Jpn J Infect Dis 2010 full article (pdf, 4 pp)

Diffuse large B-cell lymphoma involving the central nervous system. G Gualco, LM Weiss, GN Barber, CE Bacchi. Int J Surg Pathol 2011 Feb;19(1):44-50. 2 of 36 cases were positive for EBV.

Nasopharyngeal extranodal NK/T-cell lymphoma, nasal type: retrospective study of 18 consecutive cases in Guangzhou, China. YH Huang, QL Wu, YS Zong, YF Feng, JH Hou. Int J Surg Pathol 2011 Feb;19(1):51-61. "NKTCLs accounted for 69.2% (18/26) of nasopharyngeal T- and NK-cell lineage non-Hodgkin lymphomas. In all, 10 out of 18 patients (55.56%) had cervical lymph node(s) involvement. The serum anti-EBV antibody level was elevated (VCA-IgA titer ≥1:40) in 6 of 12 available patients. Two major immunophenotypic subtypes, namely, TIA-1+/EBERs+/CD56+ (10 cases) and TIA-1+/EBERs+/CD56- (8 cases) could be recognized. Genotyping analysis revealed that 10 out of 13 cases (76.9%) of NKTCL were harbored with del-LMP1 [del-LMP1 (Gly335) variant 7 cases, del-LMP1 (Asp335) variant 3 cases]. XhoI-loss was shown in 8/11 cases (72.73%). BamHI "f" variant of Bam F fragment was shown only in 4/14 cases (28.57%).The most common combination was del-LMP1 (Gly335)/ XhoI-loss/F (6/9, 66.7%)."
Vela, E Cortes, C Ortiz-Hidalgo, F Fend, L Quintanilla-Martinez. Mod Pathol 2011 Apr 15 [Epub ahead of print]. 305 diffuse large B-cell lymphomas. 7% (9 of 136) from Mexico, and 2% (4 of 169) from Germany were positive. "Only cases with EBER+ in the majority of tumor cells were regarded as EBV+ diffuse large B-cell lymphoma." Of EBV+ cases, "Twelve cases (92%) were LMP1 positive and two (15%) expressed EBNA2. An interesting finding was the high frequency of EBV type B with the LMP1 30bp deletion found in the Mexican cases (50%)."

Hofscheier - Mod Pathol 2011 abstract / PubMed

Primary intestinal T-cell and NK-cell lymphomas: a clinicopathological and molecular study from China focused on type II enteropathy-associated T-cell lymphoma and primary intestinal NK-cell lymphoma. J Sun, Z Lu, D Yang, J Chen. Mod Pathol 2011 Jul;24(7):983-992. 38 cases, 6 NK-cell and 32 R-cell. "All tumors of the NK-cell group were positive for Epstein-Barr virus encoded mRNA in the majority of tumor cells and were polyclonal according to the results of commercial BIOMED-2 T-cell receptor gene rearrangement assays."

Sun - Mod Pathol 2011 abstract / PubMed


Beltran - Am J Hematol 2011 abstract / PubMed

Clinicopathologic and Molecular Features of 122 Brazilian Cases of Nodal and Extranodal NK/T-Cell Lymphoma, Nasal Type, With EBV Subtyping Analysis. G Gualco, P Domeny-Duarte, L Chioato, G Barber, Y Natkunam, CE Bacchi. Am J Surg Pathol 2011 Aug;35(8):1195-1203. 97 cases of nasal/nasopharyngeal region and 23 cases in extranasal sites including 6 nodal cases. All were positive for EBV. "The global distribution of EBV subtypes showed predominance of strain subtype A, 89%, and subtype B, 11%. No dual infections were detected.... Striking differences among geographic regions were seen with the vast majority of EBV subtype B (86%) occurring in the south and southeast regions."


Epstein Barr virus in relation to apoptosis markers and patients' outcome in pediatric B-cell non-Hodgkin lymphoma. P Chabay, J Lara, M Lorenzetti, P Cambra, G Acosta Haab, L Aversa, E De Matteo, MV Preciado. Cancer Lett 2011 Aug 28;307(2):221-226. 40 patients. "Forty percent showed EBV expression, significantly higher among patients ≤10years (P=0.027), and associated with immunosuppression (P=0.020), but not associated apoptosis markers. However, EBV was associated with a worse event-free survival (P=0.016), particularly under immunosuppression."

Chabay - Cancer Lett 2011 abstract / PubMed

Mechanisms
Epstein-Barr Virus and methylation of the p16 gene

Arginine butyrate-induced susceptibility to ganciclovir in an Epstein-Barr induced lymphoma. SJ Mentzer, J Fingeroth, JJ Reilly, SP Perrine, DV Faller, Blood Cells Mol Dis 1998 Jun;24(2):114-123. "[A]ntiviral therapy with synthetic nucleosides such as ganciclovir are ineffective because the genes that render the virus susceptible to therapy are not expressed in EBV+ lymphomas... Arginine butyrate was not only effective in inducing EBV thymidine kinase transcription, but also acted synergistically with the antiviral agent ganciclovir to inhibit cell proliferation and decrease cell viability."


Herpesvirus-specific CD8 T cell immunity in old age: cytomegalovirus impairs the response to a coresident EBV infection. N Khan, A Hislop, N Gudgeon, M Cobbold, R Khanna, L Nayak, AB Rickinson, PA Moss. J Immunol 2004;173(12):7481-7489. "Interestingly, the effect of age upon EBV-specific responses depends upon donor CMV sero-status. In CMV seropositive donors, the magnitude of the EBV-specific immune response is stable with age, but in CMV seronegative donors, the response to EBV increases significantly with age. By contrast, the influenza-specific CD8 T cell immune response decreases with age, independent of CMV status. The functional activity of the herpesvirus-specific immune response decreases in elderly donors, although the characteristic phenotypes of CMV- and EBV-specific memory populations are retained. This demonstrates that aging is associated with a marked accumulation of CMV-specific CD8 T cells together with a decrease in immediate effector function. Moreover, infection with CMV can reduce prevailing levels of immunity to EBV, another persistent virus. These results suggest that carriage of CMV may be detrimental to the immunocompetent host by suppressing heterologous virus-specific immunity during aging."

Khan / J Immunol 2004 full article

CMV Impairs Immunity

Interferon Regulatory Factor 7 Is Associated with Epstein-Barr Virus-Transformed Central Nervous System Lymphoma and Has Oncogenic Properties. L Zhang, J Zhang, Q Lambert, CJ Der, L Del Valle, J Miklossy, K Khalili, Y Zhou, JS Pagano. J Virol 2004 Dec;78(23):12987-12995. "The expression of IRF-7 is increased in EBV-immortalized B lymphocytes compared with that in primary B cells. IRF-7 was phosphorylated and predominantly localized in the nucleus in the immortalized cells. The expression of IRF-7 was detected in 19 of 27 specimens of primary lymphomas of the human central nervous system by immunohistochemical analysis. The association between LMP-1 and IRF-7 was statistically highly significant for these specimens. An appreciable amount of the IRF-7 expressed in lymphoma cells was localized in the nucleus. Furthermore, IRF-7 promoted the anchorage-independent growth of NIH 3T3 cells. LMP-1 and IRF-7 showed additive effects on the growth transformation of NIH 3T3 cells. IRF-7-expressing NIH 3T3 cells formed tumors in athymic mice. Thus, IRF-7 has oncogenic properties and, along with LMP-1, may mediate or potentiate the EBV transformation process in the pathogenesis of EBV-associated lymphomas."

Zhang / J Virology 2004 Full Article
LMP1 strain variants: biological and molecular properties. BA Mainou, N Raab-Traub. J Virol 2006 Jul;80(13):6458-6468. "LMP1 can activate a wide array of signaling pathways, including phosphatidylinositol 3-kinase (PI3K)-Akt and NF-kappaB. Six sequence variants of LMP1, termed Alaskan, China 1, China 2, Med+, Med-, and NC, have been identified, and individuals can be infected with multiple variants. The frequencies of detection of these variants differ for various EBV-associated malignancies from different geographic regions. While all the variants activated the PI3K-Akt signaling pathway to similar extents, the Alaskan, China 1, and Med+ variants had limited binding to the E3 ubiquitin ligase component homologue of Slimb and had slightly enhanced NF-kappaB signaling."

Mainou / J Virol 2006 full article
Mainou - J Virol 2006 full article / PubMed Central

Epstein-barr virus-induced resistance to drugs that activate the mitotic spindle assembly checkpoint in Burkitt's lymphoma cells. M Leao, E Anderton, M Wade, K Meekings, MJ Allday. J Virol. 2007 Jan;81(1):248-260. "[L]atent EBV can compromise the mitotic spindle assembly checkpoint and rescue Burkitt's lymphoma (BL)-derived cells from caspase-dependent cell death initiated in aberrant mitosis. This leads to unscheduled mitotic progression, resulting in polyploidy and multi- and/or micronucleation... These data suggest that a subset of latent EBV gene products may increase the likelihood of damaged DNA being inherited because of the impaired checkpoint and enhanced survival capacity. This could lead to greater genetic diversity in progeny cells and contribute to tumorigenesis. Furthermore, since it appears that this restricted latent EBV expression interferes with the responses of Burkitt's lymphoma-derived cells to cytotoxic drugs, the results of this study may have important therapeutic implications in the treatment of some BL."

Leao / J Virol. 2007 full article
Leao - J Virol. 2007 full article / PubMed Central

A molecular link between malaria and Epstein-Barr virus reactivation. A Chêne, D Donati, AO Guerreiro-Cacais, V Levitsky, Q Chen, KI Falk, J Orem, F Kironde, M Wahlgren, MT Bejarano. PLoS Pathog 2007 Jun;3(6):e80. "We show that CIDR1alpha binds to the EBV-positive B cell line Akata and increases the number of cells switching to the viral lytic cycle as measured by green fluorescent protein (GFP) expression driven by a lytic promoter. The virus production in CIDR1alpha-exposed cultures was directly proportional to the number of GFP-positive Akata cells (lytic EBV) and to the increased expression of the EBV lytic promoter BZLF1. Furthermore, CIDR1alpha stimulated the production of EBV in peripheral blood mononuclear cells derived from healthy donors and children with BL. Our results suggest that P. falciparum antigens such as CIDR1alpha can directly induce EBV reactivation during malaria infection that may increase the risk of BL development for children living in malaria-endemic areas. To our knowledge, this is the first report to show that a microbial protein can drive a latently infected B cell into EBV replication."

Chêne / PLoS Pathog 2007 full article
Chêne - PLoS Pathog 2007 full article / PubMed Central
Epstein-Barr Virus Infection of Langerhans Cell Precursors as a Mechanism of Oral Epithelial Entry, Persistence, and Reactivation. DM Walling, AJ Ray, JE Nichols, CM Flaitz, CM Nichols. J Virol 2007 Jul;81(13):7249-7268. "In this study, we present the first evidence demonstrating that EBV latently infects a unique subset of blood-borne mononuclear cells that are direct precursors to Langerhans cells and that EBV both latently and productively infects oral epithelium-resident cells that are likely Langerhans cells. These data form the basis of a proposed new model of EBV transition from blood to oral epithelium in which EBV-infected Langerhans cell precursors serve to transport EBV to the oral epithelium as they migrate and differentiate into oral Langerhans cells. This new model contributes fresh insight into the natural history of EBV infection and the pathogenesis of EBV-associated epithelial disease."

Walling / J Virol 2007 abstract

Latent membrane protein 1 of Epstein-Barr virus activates the hTERT promoter and enhances telomerase activity in B lymphocytes. L Terrin, J Dal Col, E Rampazzo, P Zancal, M Pedrotti, G Ammirabile, S Bergamin, S Rizzo, R Dolcetti, A De Rossi. J Virol 2008 Oct;82(20):10175-10187. "In the present study, we provide evidence indicating that, in B lymphocytes, LMP1 directly promotes the activation of telomerase by acting at the transcriptional level on the hTERT promoter. These effects are mediated by engagement of the NF-κB, MAPK, and ERK1/2 pathways." LMP1 transactivates the hTERT promoter in both epithelial and B cells.

Terrin - J Virol 2008 full article / PubMed Central

Nucleoside diphosphate kinase/Nm23 and Epstein-Barr virus. M Murakami, R Kaul, P Kumar, ES Robertson. Mol Cell Biochem 2009 Sep;329(1-2):131-139. "Nm23-H1 was discovered as the first metastasis suppressor gene about 20 years ago... EBNA3C and EBNA1, required for EBV-mediated lymphoproliferation and for maintenance EBV genome extrachromosomally in dividing mammalian cells, respectively, target and disrupt the physiological role of Nm23-H1 in the context of cell proliferation and cell migration."

Murakami - Mol Cell Biochem 2009 abstract / PubMed

Three Epstein-Barr virus latency proteins independently promote genomic instability by inducing DNA damage, inhibiting DNA repair and inactivating cell cycle checkpoints. B Gruhne, R Sompallae, MG Masucci. Oncogene 2009 Nov 12;28(45):3997-4008. "EBV nuclear antigens, EBNA-1 and EBNA-3C, and the latent membrane protein 1, LMP-1, independently promote genomic instability, as detected by nonclonal chromosomal aberrations, DNA breaks and phosphorylation of histone H2AX. EBNA-1 promotes the generation of DNA damage by inducing reactive oxygen species (ROS), whereas DNA repair is inhibited in LMP-1-expressing cells through downregulation of the DNA damage-sensing kinase, ataxia telangiectasia mutated (ATM), reduction of phosphorylation of its downstream targets Chk2 and inactivation of the G2 checkpoint. EBNA-3C enhances the propagation of damaged DNA through inactivation of the mitotic spindle checkpoint and transcriptional downregulation of BubR1."

Gruhne - Oncogene 2009 abstract / PubMed
Epigenetic repression of p16\(^{INK4A}\) by latent Epstein-Barr Virus requires the interaction of EBNA3A and EBNA3C with CtBP. L. Skalska, R.E. White, M. Franz, M. Ruhmann, M.J. Allday. PLoS Pathog 2010;6(6): e1000951. "[C]hromatin remodelling and epigenetic repression of p16INK4A requires the interaction of both EBNA3A and EBNA3C with CtBP. The repression of p16INK4A by latent EBV will not only overcome senescence in infected B cells, but may also pave the way for p16INK4A DNA methylation during B cell lymphomagenesis."

Skalska / PLoS Pathog 2010 full article

Micro RNAs of Epstein-Barr Virus Promote Cell Cycle Progression and Prevent Apoptosis of Primary Human B Cells. E. Seto, A. Moosmann, S. Grömminger, N. Walz, A. Grundhoff, W. Hammerschmidt. PLoS Pathog 2010;6(8):e1001063. "To assess the roles of EBV's miRNAs in this model, we generated EBV mutants that lack the capacity to encode viral miRNAs. Phenotypic analysis of human primary B cells infected with these mutant viruses revealed that miRNAs encoded in EBV's BHRF1 locus strongly promote B cell proliferation, regulate cell cycle functions, and prevent apoptosis early after infection."

Seto / PLoS Pathog 2010 full article


Ma - J Virol 2011 abstract / PubMed

Epstein-Barr virus nuclear antigens 3C and 3A maintain lymphoblastoid cell growth by repressing p16INK4A and p14ARF expression. S. Maruo, B. Zhao, E. Johannsen, E. Kieff, J. Zou, K. Takada. Proc Natl Acad Sci USA 2011 Feb 1;108(5):1919-1924. "In the absence of EBNA3C or EBNA3A, p16(INK4A) and p14(ARF) expression increased and cell growth ceased. EBNA3C inactivation did not alter p16(INK4A) promoter CpG methylation, but reduced already low H3K27me3, relative to resting B cells, and increased H3K4me3 and H3-acetylation, linking EBNA3C inactivation to histone modifications associated with increased transcription."

Maruo - Proc Natl Acad Sci USA 2011 abstract / PubMed

The H3K27me3 demethylase, KDM6B, is induced by Epstein-Barr virus and over-expressed in Hodgkin's Lymphoma. J.A. Anderton, S. Bose, M. Vockerodt, K. Vrzalikova, W. Wei, M. Kuo, K. Helin, J. Christensen, M. Rowe, P.G. Murray, C.B. Woodman. Oncogene 2011 Apr 28;30(17):2037-2043. "KDM6B is over-expressed in primary HL and induced by the EBV oncogene, latent membrane protein (LMP1) in GC B cells, the presumptive progenitors of HL. Consistent with these observations, we found that..."
KDM6B transcriptional targets in GC B cells are enriched for genes differentially expressed in HL, and that KDM6B depletion can restore the tri-methylation of H3K27 on these genes."

Anderton - Oncogene 2011 abstract / PubMed

Specific infiltration of langerin-positive dendritic cells in EBV-infected tonsil, Hodgkin lymphoma and nasopharyngeal carcinoma. PH Braz-Silva, S Vitale, C Butori, N Guevara, J Santini, M Magalhães, P Hofman, A Doglio. Int J Cancer 2011 May 1;128(10):2501-2508. "We report here the existence of a novel subset of langerin (CD207)-positive, immature dendritic cells (DCs) (CD83(neg)) abundantly infiltrating Epstein Barr virus (EBV)-infected areas in tonsil, Hodgkin lymphoma and nasopharyngeal carcinoma. These CD207(+) DCs differ from conventional epidermal Langerhans cells in their lack of CD1a and CCR6 and their unusual tissue localization. CD207(+) DC infiltration strongly correlates with EBV infection because it was neither detected in EBV negative specimens nor in tissues infected with other human viruses. These immature DCs might represent good candidates for induction of the EBV-specific immune response."

Braz-Silva - Int J Cancer 2011 abstract / PubMed

The Epstein-Barr virus nuclear antigen-1 promotes telomere dysfunction via induction of oxidative stress. SA Kamranvar, MG Masucci. Leukemia 2011 Jun;25(6):1017-1025. "Stable or conditional expression of EBNA1 induced telomere abnormalities including loss or gain of telomere signals, telomere fusion and heterogeneous length of telomeres. This was accompanied by the accumulation of extrachromosomal telomeres, telomere dysfunction-induced foci (TIFs) containing phosphorylated histone H2AX and the DNA damage response protein 53BP1, telomere-associated promyelocytic leukemia nuclear bodies (APBs), telomeric-sister chromatid exchanges and displacement of the shelterin protein TRF2."

Kamranvar - Leukemia 2011 abstract / PubMed
Kamranvar - Leukemia 2011 full article / PubMed Central

Epigenetic and transcriptional changes which follow Epstein-Barr virus infection of germinal centre B cells and their relevance to the pathogenesis of Hodgkin's lymphoma. S Leonard, W Wei, J Anderton, M Vockerodt, M Rowe, PG Murray, CB Woodman. J Virol 2011 Jul 13 [Epub ahead of print]. "We show that EBV infection of GC B cells is followed by up-regulation of the DNA methyltransferase, DNMT3A and down-regulation of DNMT3B and of DNMT1. We show that the EBV oncogene, LMP1, down-regulates DNMT1, and that DNMT3A binds to the viral promoter Wp. Genome-wide promoter arrays performed on these cells showed that EBV-associated methylation changes in cellular genes were not randomly distributed across the genome but clustered at chromosomal locations consistent with an instructive pattern of methylation and were in part determined by promoter CpG content. Both DNMT3B and DNMT1 were down-regulated and DNMT3A up-regulated in HL cell lines, recapitulating the pattern of expression observed following EBV infection of GC B cells. We also found using gene expression profiling, that genes differentially expressed following EBV infection of GC B cells were significantly enriched for those reported to be differentially expressed in
HL. These observations suggest that EBV-infected GC B cells are a useful model for studying virus associated changes contributing to the pathogenesis of HL.