Epstein-Barr Virus

CAS No.: none assigned

Known to be a human carcinogen

Also known as EBV or human herpesvirus 4 (HHV-4)

Carcinogenicity

Epstein-Barr virus (EBV) is *known to be a human carcinogen* based on sufficient evidence from studies in humans. This conclusion is based on evidence from epidemiological, clinical, and molecular studies, which show that Epstein-Barr virus causes endemic Burkitt lymphoma, Hodgkin lymphoma, immune-suppression-related non-Hodgkin lymphoma, nasal-type extranodal natural killer (NK)/T-cell lymphoma, nasopharyngeal carcinoma, and some forms of stomach cancer. There is also limited evidence for an association between EBV and sporadic Burkitt lymphoma. Results from clinical and mechanistic studies indicate that in EBV-infected B lymphocytes (a type of immune cell), EBV viral proteins are produced while the virus is latent (i.e., while the virus persists in cells without destroying them). These proteins (including latent membrane protein 1 [LMP-1] and Epstein-Barr nuclear antigens [EBNA-1, 2, 3A, and 3C]) enable the infected B lymphocytes to survive and proliferate indefinitely, leading to cancer in some cases. The specific protein involved in carcinogenicity may vary with the cancer end point. Furthermore, in most EBV-related cancers, a large proportion of tumor cells contain viral DNA that is derived from a single ancestral virus particle (i.e., monoclonal), suggesting that the viral infection preceded the tumor.

Cancer Studies in Humans

EBV was the first cancer-causing (oncogenic) virus to be discovered in humans; its association with Burkitt lymphoma was recognized over 50 years ago (Epstein *et al.* 1964). Burkitt lymphoma is a cancer of the immune cells with three subtypes; two of these, the endemic variant, which occurs primarily in children in equatorial Africa and Papua, New Guinea, and the sporadic variant, which is found throughout the world, are discussed here. Since the 1960s, numerous studies have explored the relationship of EBV to various other types of cancer, primarily other types of lymphoma — Hodgkin lymphoma and rare types of non-Hodgkin lymphoma (those related to immunosuppression or developing in NK or T cells in the nasal cavity) — and tumors arising from epithelial tissue, such as nasopharyngeal cancer and stomach cancer.

Burkitt Lymphoma

Evidence for an association between EBV infection and endemic Burkitt lymphoma is based on consistent findings of increased risk in several case-control and cohort studies and the presence of an exposure-response relationship with viral infection. Twelve case-control studies and a cohort study found statistically significant positive relationships between EBV infection and endemic Burkitt lymphoma, with risk increased by 3-fold to 52-fold. Moreover, several of the case-control studies and the cohort study found increasing risk of endemic Burkitt lymphoma with increasing viral load (primarily by measurement of antibodies to the viral protein VCA, viral capsid antigen) (Henle *et al.* 1969, 1971, Carpenter *et al.* 2008, Mutalima *et al.* 2008). Epidemiological evidence for an association between EBV infection and sporadic Burkitt lymphoma is somewhat weaker: positive associations were found in four of five case-control studies, one of which was statistically significant, and no studies evaluated exposure-response relationships. These studies had limited power to detect an effect because of the small numbers of EBV-infected case and control subjects.

These findings are supported by studies of human tumor tissue. EBV has been found in approximately 95% of endemic Burkitt lymphomas (Thompson and Kurzrock 2004) and in approximately 20% of sporadic Burkitt lymphomas (IARC 1997). The key event in the development of Burkitt lymphoma is a chromosomal translocation of *c-myc* (a regulatory gene) to the locus of an immunoglobulin gene promoter, which results in unregulated and persistent expression of *c-myc* RNA and proteins, which in turn regulate other genes, leading to proliferation and growth of B lymphocytes. In addition, Burkitt lymphomas infected with EBV produce a protein (EBNA-1) that plays a role in the prevention of apoptosis (programmed cell death) and enables cell survival (Lu *et al.* 2011, Kennedy *et al.* 2003).

Individuals infected with malaria in addition to EBV have been shown to have a higher risk of Burkitt lymphoma than individuals infected only with EBV. Malarial infection increases the numbers of mature B lymphocytes, many of which have chromosome damage, including EBV-induced chromosomal translocations (Robbiani *et al.* 2015). This reduces the ability of T lymphocytes to recognize and destroy infected cells and thus increases the viral load of EBV in infected individuals (Moormann *et al.* 2009).

Hodgkin Lymphoma

Evidence for an association between EBV infection and Hodgkin lymphoma is based on consistent findings of statistically significant increased risk in numerous case-control and cohort studies. The strongest evidence for an association comes from the collective findings of over 25 case-control studies, which found that Hodgkin lymphoma patients were generally 4 to 19 times more likely to have a high viral load (as measured by antibodies against viral proteins or, to a lesser extent, EBV DNA) than were individuals without Hodgkin lymphoma (NTP 2016). In a cohort study, individuals with higher levels of various types of EBV antibodies were approximately 3 to 4 times (depending on the specific antibody) more likely to develop Hodgkin lymphoma than those with lower levels of antibodies (IARC 1997, 2012). Most of the 11 case-control studies and 7 cohort studies using infectious mononucleosis as a surrogate for EBV infection also found statistically significant increased risks for Hodgkin lymphoma, though lower (generally between 1.3 and 3.0) than the risks found in the case-control studies with direct measurements of EBV infection (IARC 1997, 2012, Linabery *et al.* 2014). A few studies did not find a positive association, and not all studies found significantly increased risk. However, the strength of the database (i.e., the large number of studies using different study designs, conducted in different geographical locations, and measuring EBV by different methods) and the consistent findings of a relatively large, statistically significant increased risk, provide evidence that EBV infection causes Hodgkin lymphoma.

These findings are supported by molecular studies of human tissue or cell lines. Some forms of Hodgkin lymphoma are associated with monoclonal EBV infection. Hodgkin Reed-Sternberg cells are cancerous lymphocytes that contain EBV DNA and produce the viral proteins LMP-1 and -2A. These proteins promote growth and survival of the cancer cells by enhancing several molecular pathways (such as the NF-κB, JAK/STAT, MAP kinase, and PI3-kinase/AKT pathways), resulting in a release of cytokines (proteins that affect communication and interaction between cells) that causes a local inflammatory response (IARC 1997, 2012, Mohamed *et al.* 2014).

Immune-Suppression-Related Non-Hodgkin Lymphoma

Evidence that immune-suppression-related non-Hodgkin lymphoma is associated with EBV infection comes primarily from case series, a nested case-control study, and clinical studies showing the presence of EBV in these tumors. EBV has been found in lymphoma patients with various types of immunosuppression, including all cases of lymphoma in patients with congenital immune deficiency, almost all cases of non-Hodgkin lymphoma of the central nervous system in patients with HIV-1, and 50% of organ-transplant recipients with post-transplant lymphoproliferative disease (IARC 1997, 2012). In one study, EBV DNA was detected in the blood plasma of all patients with post-transplant lymphoproliferative disease but not in 35 healthy control subjects (Lei *et al.* 2000). A small nested case-control study found an association (although not statistically significant) between EBV antibodies and an increased risk of non-Hodgkin lymphoma in HIV-1-positive patients participating in a trial of antiretroviral therapy (Newton *et al.* 2006). Other studies in humans have shown that the EBV DNA in the tumors is monoclonal and produces oncogenic viral proteins (LMP-1, -2A, and -2B and EBNAs) that promote cell division, cell survival, and transformation into cancer cells. Finally, treatment of immune-suppressed patients with T cells sensitized to EBV has been shown to reduce viral load and reduce or protect against the formation of this tumor (Taylor *et al.* 2005, Vegso *et al.* 2011, IARC 2012).

Extranodal NK/T Cell Lymphoma, Nasal Type

Evidence that this type of lymphoma is associated with EBV infection comes primarily from more than a dozen case-series studies, with over 400 cases (IARC 1997, Barrionuevo *et al.* 2007, He *et al.* 2007), in which EBV was detected in 100% of the tumors. Nasal-type extranodal NK/T-cell lymphoma most commonly develops in NK cells, but can also occur in cytotoxic T cells. Two studies found EBV DNA in the blood plasma or CD3+ (T) cells from patients with this type of lymphoma, but not from healthy control subjects (Lei *et al.* 2000, Suwiwat *et al.* 2007). Other studies in humans have shown that the EBV DNA in the individual tumors is monoclonal and produces several viral proteins (LMP-1 and -2A and EBNA-1) involved in tumor development (IARC 2012).

Nasopharyngeal Carcinoma

Evidence for an association between EBV infection and nasopharyngeal carcinoma is based on consistent findings of highly increased risk in numerous case-control and cohort studies conducted largely in Southeast Asia, and also in Europe, North Africa, and the United States. The strongest evidence comes from the collective findings of 11 case-control studies, all of which reported statistically significant increased risks for this type of cancer, with most risk estimates ranging from 21 to 138 in studies measuring EBV antibody, and 41 to 820 in the studies measuring EBV DNA or DNase (an enzyme that degrades DNA). Increased risks were also found in two cohort studies (totaling 168 cases with up to 16 years of follow-up) but not in two small nested case-control studies, one among Alaska Natives in the United States (where nasopharyngeal cancer is rare) and the other among the general U.S. population. Other studies reported significantly higher mean EBV viral loads in case subjects than in control subjects (IARC 1997, 2012, NTP 2016).

These findings are supported by data from molecular studies. Monoclonal forms of EBV DNA are found in precancerous lesions and with 98% of non-keratinizing nasopharyngeal carcinomas, indicating that viral infection is an early event in cancer progression (Pathmanathan *et al.* 1995, Liu *et al.* 2011, Tsang *et al.* 2014, Tsao *et al.* 2015), and EBV has been shown to produce viral proteins (LMP-1 and -2A and EBNA-1) involved in carcinogenesis (Raab-Traub 2002).

Stomach (Gastric) Cancer

Epidemiological, case-series, clinical, and molecular studies provide evidence for an association between EBV infection and a specific type of stomach cancer. EBV is found in 8% to 11% of stomach tumors, and EBV-related tumors are more likely than other types of stomach tumors to originate in the gastric cardia (where the contents of the esophagus empty into the stomach), the main body of the stomach, or a gastric stump (the portion of the stomach remaining after partial removal). Statistically significant positive associations between EBV infection (as measured by either antibodies to viral proteins or EBV DNA) and stomach cancer were found in three case-control studies (Shinkura *et al.* 2000, Lo *et al.* 2001, De Aquino *et al.* 2012). Positive associations were also seen in two of three nested case-control studies (Levine *et al.* 1995, Kim *et al.* 2009), but the results were not statistically significant.

Molecular studies provide strong evidence of an association between EBV and some stomach cancers. Monoclonal forms of EBV DNA are found in a subset of human stomach cancers and produce several viral proteins (LMP-1 and -2A and EBNA-1) involved in tumor development. EBV-infected stomach tumors have a unique molecular profile characterized by (1) changes in the DNA chemistry of the tumor-suppressor gene *CDKN2A+* (specifically, addition of methyl groups to control gene expression), resulting in reduced production of two other tumor-suppressor proteins (p16 and 14), (2) mutations in the oncogene *PIK3CA,* and (3) increased numbers of copies of genes involved in cell growth and division (JAK2) and immune suppression (oncogenes *CD274* and *PDCD1LG2*) (Cancer Genome Atlas Research Network 2014, Gulley 2015).

Studies on Mechanisms of Carcinogenesis

Direct evidence that EBV causes lymphoma comes from studies of human cells *in vitro* and of mice *in vivo*. EBV has been shown to transform B lymphocytes into permanently infected lymphoblastoid cell lines in culture (Young and Rickinson 2004) and to transform human epithelial cells co-cultured with cells derived from an EBV-infected Burkitt lymphoma tumor (Imai *et al.* 1998). In addition, EBV-infected B lymphocytes caused B-cell lymphoma in mice with compromised immune systems (Mosier *et al.* 1989, Rowe *et al.* 1991). Normally, newly mature B lymphocytes that are defective are destroyed by undergoing programmed cell death; however, *in vitro* studies have shown that the viral protein EBNA-1 prevents defective B cells from undergoing apoptosis by directly enhancing production of the apoptosis-inhibiting protein survivin (Lu *et al.* 2011) (see also NTP 2016).

Biological Properties

Epstein-Barr virus is an enveloped double-stranded DNA gamma-1 herpesvirus (IARC 2012). The 172-kb EBV genome encodes over 85 genes, categorized as latent or lytic: latent genes are expressed while the virus is dormant, and lytic genes are expressed during the lytic cycle, when the virus replicates and destroys the infected host cell. The two major types of EBV (EBV-1 and EBV-2) differ in the DNA sequences of the genes encoding their nuclear antigens (EBNA-2, -3A, -3B), and each type has several strains. Infection of epithelial cells is primarily lytic, whereas infection of B cells is primarily latent. However, antibody-producing B cells allow EBV to enter the lytic phase and replicate (Ponce *et al.* 2014). EBV proteins produced on the membranes of infected cells in most stages of latency can be recognized by cytotoxic T cells and NK cells, which attack and destroy them (Thorley-Lawson and Gross 2004). However, EBV in latency 0 phase, typically found in resting memory B cells (B lymphocytes sensitized to respond to specific antigens), does not produce proteins on the membranes of infected cells, thereby allowing EBV to evade recognition by the immune system.

Detection

EBV infection can be detected by measuring anti-EBV antibodies in serum or EBV DNA or RNA in peripheral white blood cells (IARC 2012). Measurement of EBV DNA or RNA can indicate EBV viral load, reactivation, response to treatment, and presence in tumor cells. Methods for detection of EBV DNA and RNA include quantitative polymerase chain reaction (PCR), reverse-transcriptase PCR, or *in situ* hybridization. Healthy carriers of EBV do not have detectable EBV DNA or RNA in cell-free serum, so positive results indicate EBV-associated disease or EBV reactivation.

Exposure

Studies measuring antibodies to EBV in blood serum have shown that a significant number of people in the United States are infected with EBV. EBV seroprevalence in the United States, based on National Health and Nutrition Examination Survey data collected in 2009 and 2010, ranged from 50% in 6- to 8-year-olds to 89% in 18- to 19-year-olds (Balfour *et al.* 2013, Dowd *et al.* 2013). Worldwide, more than 90% of adults are infected with EBV (IARC 2012).

Transmission

Transmission of EBV is mainly via saliva, despite the fact that the virus does not infect the salivary glands (IARC 2012). The presence of EBV in peripheral blood suggests that transmission via blood also is possible, and transmission has been reported among transfusion and organ-transplant recipients. Infected cells, primarily resting memory B cells in peripheral blood, provide a permanent reservoir from which progeny viruses can disseminate within the body and infect other people. EBV transmission via breast milk (Daud *et al.* 2015) and genital secretions (Thomas *et al.* 2006) has also been reported.

Age at primary infection varies, occurring at a higher rate during infancy in middle- to low-income countries than in high-income countries, perhaps as a result of better hygienic conditions and other socioeconomic and demographic factors that result in later age of exposure to infected saliva (e.g., household size and population density) (Biggar *et al.* 1978a,b, IARC 2012, Piriou *et al.* 2012, Dowd *et al.* 2013). Similar patterns of lower infection rates (as inferred by seroprevalence) with higher socioeconomic status within race and ethnicity groups are observed in the United States. An analysis of 782 serum samples from Minnesota children aged 18 months to 19.9 years indicated that a combination of genetics, family practices, and home environment were responsible for racial and ethnic differences in EBV prevalence among young children. The route of EBV transmission to preadolescents remains unclear (Condon *et al.* 2014).

Diseases (Non-Cancer), Prevention, and Treatment

Most individuals are infected with EBV but remain otherwise healthy and without symptoms (IARC 2012). Infection is lifelong and has no noticeable symptoms when it occurs in early childhood (IARC 2012); however, it results in infectious mononucleosis in at least 25% of infected teenagers and young adults (CDC 2014b). Oral hairy leukoplakia (a disease of the mucous membranes causing white patches on the tongue) results from infection with EBV in the context of impaired immune function, such as immunosuppression caused by HIV-1 or deterioration of the immune system with normal aging (immunosenescence) (Auwaerter 2015). Chronic active EBV occurs frequently in Asia and South America, but rarely in the United States and Europe. Its etiology is unknown, but is believed to involve rare genetic abnormalities that impair immune control of EBV infection (Rigaud *et al.* 2006, Cohen 2009, Chaigne-Delalande *et al.* 2013). EBV has also been suggested as a cause of rare autoimmune diseases affecting the liver, including autoimmune hepatitis (Rigopoulou *et al.* 2012).

EBV transmission is associated with EBV shedding in saliva; therefore, avoiding salivary exposure (e.g., via kissing or sharing food, drink, or toothbrushes) may theoretically prevent transmission (CDC 2014a).

Some drugs have been reported to reduce or inhibit EBV shedding (e.g., Auwaerter 2015); however, no FDA-approved drugs currently exist for treatment of EBV infection. There is no vaccine against EBV, but vaccine development efforts are ongoing (Balfour 2014, ACS 2015, CDC 2015, Cohen 2015, FDA 2015).

Regulations

Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA)

21 CFR 866 identifies Epstein-Barr virus serological reagents (i.e., devices that consist of antigens and antisera used in serological tests to identify antibodies to EBV in serum) as Class I medical devices requiring premarket notification for FDA clearance to market.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Guidelines

Food and Drug Administration (FDA, an HHS agency)

The FDA has issued numerous guidance documents prescribing procedures (e.g., use of standardized labels, abbreviated donor screening questionnaires) for reducing the risk of virus transmission by blood and blood products.

Health Resources and Services Administration (HRSA, an HHS agency)

The Organ Procurement and Transplantation Network (OPTN) prescribes voluntary procedures for donor screening, recordkeeping, notification (e.g., recipient informed consent), and, as appropriate, posttransplant preventive interventions or monitoring and testing procedures to guard against the spread of EBV through solid (vascular) organ transplantation.

American Society of Transplantation (AST)

The AST recommends that EBV serology be performed on all donors and recipients in order to define the risk of posttransplant lymphoma. The AST has issued guidance for the use of solid organs from donors testing positive for EBV and subsequent management of recipients of such organs. No limits are proposed for transplants between donors and recipients who are both EBV positive. AST does advise that EBV-negative recipients of EBV-positive organs be considered for posttransplant nucleic acid test monitoring for EBV to help guide immunosuppression, because they are at a higher risk for primary EBV infection and posttransplant lymphoproliferative disease.

American Red Cross (ARC)

American Red Cross donor eligibility guidelines prohibit blood donation by potential donors who have had hepatitis caused by a virus or unexplained jaundice since age 11, including those who had hepatitis with cytomegalovirus or EBV.

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