

Gammaherpesvirinae

- **Lymphocryptovirus (HHV4/EBV)**
- **Rhadinovirus (HHV8)**

EPSTEIN-BARR VIRUS

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- **EBV was first isolated in 1964 from tumour samples taken from patients with Burkitt's lymphoma.**
- **1968 shown to be a common cause of infectious mononucleosis in adolescents**
- **Envelope and tegument proteins differ in size from other herpesviruses.**
- **First herpesvirus whose genome was completely cloned and sequenced.**
- **Two EBV types (A & B) circulate in most human populations**

EPSTEIN-BARR VIRUS

- **2 types A & B (differ in EBNA 2 gene)**
 - **type A most common in US & Europe isolated from B lymphocytes**
 - **type B only recovered from immunocompromised patients**
- **Most limited host range of all herpesviruses**
- **Responsible for lymphomas and carcinomas in a wide range of species**

EPSTEIN-BARR VIRUS EPIDEMIOLOGY

- **EBV persists in the population through sporadic shedding via the oropharynx into saliva.**
- **Infection normally occurs after 10 yrs of age.**
- **Infection during adolescence usually results in IM**
- **40 – 65% of adults have antibodies to EBV**

EPSTEIN-BARR VIRUS CLINICAL

Normal Host

- **Subclinical infection in infants >2 years old**
- **Infectious Mononucleosis (glandular fever) in adolescents**
 - 4-7 week incubation
 - insidious onset and vague clinical presentation
 - fluctuating fever, pharyngitis, lymphadenopathy, spleen enlarged and liver affected
- **Illness usually persists for several weeks, and rarely beyond several months. An association with CFS has been proposed but not proven.**

EPSTEIN-BARR VIRUS CLINICAL

Immunocompromised Host

- **Unrestrained EBV replication**
 - any organ system can be affected; lungs & liver
 - B-cell lymphomas in some T-cell deficient genetic disorders
- **Pneumonitis and CNS disease are rare.**

The kiss of cancer

Named after its discoverers, Epstein–Barr virus (EBV) was first isolated in 1964 from patients with hematologic pathology. It is a lymphocytic human herpesvirus that is carried, like some other pathogenic herpesviruses, by the majority of the world's population as a persistent, latent contagious agent.

EBV is usually transmitted orally, and it may cause infectious mononucleosis in adolescents and young adults. *EBV was also found in several malignancies such as Hodgkin's lymphoma (or Hodgkin's disease) and carcinomas, as well as in some immunodepressed pathologies like AIDS. This oncovirus is also responsible for a lymphoma-resembling disease in New World primates.*

Despite the evidence of EBV's contribution to the etiology of Hodgkin's disease, the real causes of malignancy are still unclear. Moreover, the long-term risk of this and other cancers following the occurrence of infectious mononucleosis remains poorly characterized.

In a large-scale cancer study among Danish and Swedish patients, a team of Scandinavian researchers came to the conclusion that *there is a substantial increase in the risk of Hodgkin's disease for up to two decades after the diagnosis of infectious mononucleosis* (*J. Natl. Cancer Inst.* **2000**, *92*, 1522–1528). In addition, the study showed that following about of infectious mononucleosis, skin cancers are the only malignancies that occur with increased frequency. In contrast, the risk of lung cancer is significantly reduced.

EPSTEIN-BARR VIRUS CLINICAL

Neoplasms - Burkitt's lymphoma

- **Burkitt's lymphoma is the most common childhood malignancy in equatorial Africa & PNG (80% of childhood cancers)**
- **EBV was detected in tumour tissues from these patients**
- **Area is also endemic for malaria. Continuous infection with malaria causes polyclonal B cell stimulation and together with rampant malnutrition, suppresses T cell responses. This results in a greater number of EBV-infected proliferating B cells which increases the probability of development of cytogenetic abnormalities**

EPSTEIN-BARR VIRUS CLINICAL

Neoplasms - Nasopharyngeal carcinoma

- **Nasopharyngeal carcinoma due to EBV is rare in Europeans but common in southern China. Etiological factors include EBV, genetic susceptibility and environmental factors.**
- **Most common cancer in China & eskimos**
- **up to 40 years between infection & cancer**
- **EBNA-1 expression is upregulated**
- **Ethnic restriction - genetic predilection or dietary cofactor**

EPSTEIN-BARR VIRUS CLINICAL

Neoplasms - Other

- **B-cell Lymphoproliferative disease may also occur post-transplantation or in HIV-infected patients and is potentially fatal.**
- **EBV induced CNS lymphoma and non-Hodgkin's lymphoma are major cause of death in AIDS patients**

EPSTEIN-BARR VIRUS DIAGNOSIS

- **Isolation of infectious** virus from peripheral blood mononuclear cells is the most definitive method of diagnosing primary infection. However special cell culture techniques need to be applied. Not often performed.
- Diagnosis of IM is best accomplished by **examining the IgM and IgG antibody reactivity** pattern to a number of EBV proteins. These include the viral capsid (VCA), nuclear protein (EBNA) and the leader protein (EBNA LP)
- Virus in tumour biopsy specimens is detected by direct **immunofluorescence or by PCR** amplification.

HUMAN HERPESVIRUS - 8

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- **First detected in 1995 in Kaposi sarcoma biopsies from AIDS patients.**
- **DNA sequences detected by differential PCR. Virus was not isolated or visualised.**
- **Genome sequence analysis identified a new herpesvirus classified as a gamma-herpesvirus**
- **Contains a “pirated oncogenic cluster” of cellular genes**

HUMAN HERPESVIRUS - 8

- Closely associated with KS, but now shown to be more widespread. Found in biopsies of body cavity lymphomas (Castleman's Disease).
- Castleman's disease is a rare B cell lymphoproliferative disorder related to excess IL-6 activity.
- HHV-8 encodes for a cytokine IL-6 homologue which leads to B cell lymphoproliferation.
- Diagnosis by PCR using specific primers.