

The Epstein-Barr Virus: Background and Summary of Article

by
Jamie A. Singleton

College of Medicine Class of 2007
Medical University of South Carolina
Molecular Basis of Medicine Treatise

Abstract

The purpose of this paper is to summarize an article about the Epstein-Barr virus entitled *Epstein-Barr Viral Gene Expression in B-Lymphocytes*. Before doing so, information about the virus will be presented. The Epstein-Barr virus (EBV) is a member of the herpesvirus family; it is herpesvirus IV. EBV is very common, infecting over ninety-five percent of the adults between the ages of thirty-five and forty. EBV is known to cause Infectious Mononucleosis and is a known human tumor virus. The article was written to determine if B-Lymphocytes differ with respect to lytic replication and to determine if B-lymphocytes reactivate in peripheral blood. To test both of these hypotheses RT-PCR of CD-19 positive cells were used. It was found that there was no difference in B-Lymphocytes with respect to replication and that blood only allowed reactivation to proceed to a certain stage.

Singleton, Jamie A. The Epstein-Barr Virus: Background and Summary of Article. South Carolina Journal of Molecular Medicine (SCJMM) 5:40-43; 2004.

Author's Addresses:
singlej@musc.edu

The manuscript has been seen and approved by the author and the editor.

Purpose

The purpose of this paper is to summarize an article about the Epstein-Barr virus entitled *Epstein-Barr Viral Gene Expression in B-Lymphocytes*. Before doing so, information about the virus will be presented.

Background

The Epstein-Barr virus (EBV) is a member of the herpesvirus family; it is herpesvirus IV. EBV is very common, infecting over ninety-five percent of the adults between the ages of thirty-five and forty. Nonetheless, infection can occur once maternal antibody protection has disappeared ("Epstein-Barr Virus"). The age of infection is closely related to socioeconomic class. In underdeveloped nations transmission of the

virus generally occurs at an early age, usually during the first year of life (Roizman et. al. 142). On the other hand, in more developed nations, transmission is more likely to occur between the ages of fifteen and twenty-five (Schlossberg 19). This trend exists because the virus is transmitted by close oral contact, which allows for the exchange of saliva, and this exchange, is more likely to happen in children with a poor socioeconomic background than it is in children with a rich socioeconomic background (Schlossberg 18).

Infectious Mononucleosis

EBV is known to cause Infectious Mononucleosis (IM). However this occurs in infections only thirty five to fifty percent

of the time (“Epstein-Barr Virus”). IM is less common in underdeveloped countries because EBV is asymptomatic in young children; they have a silent seroconversion. However, after the age of fifteen, seroconversion is less likely to be asymptomatic and thus there is a higher incidence of IM (Schlossberg 19). IM is known as the “Kissing Disease” because as stated earlier, the main route of transmission is through saliva. However, it can also be spread through blood and the air, although this is highly unusual. The symptoms include fever, sore throat, headache, malaise, and enlarged tonsils. The infection may also be associated with an enlarged spleen and/or liver. Symptoms may not appear for four to six weeks from the primary infection and although IM is usually never fatal, symptoms can last from one to two months (“Epstein-Barr Virus”).

Once symptoms are gone the virus lives dormant in B-lymphocytes and oropharyngeal epithelial cells as episomes and are passed to new generations of cells during cell division. The virus may reactivate asymptotically. Reactivation only occurs in the epithelial cells. These cells in turn infect B-lymphocytes as they circulate through the oropharynx. At this time, person-to-person transmission is possible (Winnie).

EBV and Tumors

The virus is also known to be the cause of rare tumors such as Nasopharyngeal carcinoma (NPC) and Burkitt’s lymphoma (BL). NPC is a lymphoid stroma. It is rare in the US, yet it is one of the most popular cancers in southern China. Studies indicate that genetics and environment may play a role in the high incidence of NPC in southern China (Roizman et. al. 149). Symptoms of NPC usually include a lump in the neck, nasal obstruction, and hearing loss (“Nasopharynx Cancer”).

Burkitt’s lymphoma is a non-Hodgkin’s type of lymphoma that is similar to leukemia and infects B-lymphocytes. This cancer is rare in the US, only 300 cases a year, however it is the most common cancer in Central Africa. It grows rapidly and usually effects children (Burkitt’s).

History

To follow the history of the Epstein-Barr virus one must first study the history of Infectious Mononucleosis. Due to the fact that EBV is asymptomatic in children and that most of the population lived in low socioeconomic conditions, IM was virtually unknown (Schlossberg 25). It wasn’t until the late nineteenth century that the symptoms were noticed and then it was described as glandular fever. In 1920, Sprunt described the disease and named it Infectious Mononucleosis. Diagnostic procedures were first described in 1923 by Downey who explained lymphocyte morphology. Then in 1932 Paul and Bunnell showed that serum from IM patients had heterophile antibodies. Still at this time there was no etiologic agent for IM because researchers didn’t realize that most of the primary infections were asymptomatic. Then in 1964 Epstein and Barr described the first human tumor virus when they isolated EBV from a Burkitt’s lymphoma cell line. Still it wasn’t until 1968 that Henel made the correlation between EBV and IM (Winnie).

Summary of Article

Preface

The article is entitled *Epstein-Barr Viral Gene Expression in B-Lymphocytes*. It was written by Fritz Schwarzmann, et. al. and is published in the thirtieth volume of Leukemia and Lymphoma. The article will be presented in the order it is written.

Introduction

The Epstein-Barr virus evades the immune system of the host in two ways. The first is to replicate fast. This will allow the virus to produce enough offspring to ensure that some will survive the immune system. The second way is to lie dormant in the cell for life. With the first way, the virus has to hide from the immune system until it can replicate. This is done by spatial separation of dormant existence and lytic replication.

B-Lymphocytes Are a Major Source of EBV During IM

The primary site of entry for EBV is oropharyngeal mucosa. The primary infection is either asymptomatic or it presents as IM. During this time antibodies that indicate that the virus is replicating will appear.

There has been no research to unequivocally identify the primary cell that is used during replication. Research has shown that skin cells allow lytic replication in vivo, but other studies have shown replication in the absence of skin cells. Still, B-Lymphocytes are only latently infected during IM and in healthy individuals; these findings contrast findings in oral mucosa.

Thus “to investigate whether [B-Lymphocytes] in oropharyngeal epithelium are different from those in peripheral blood with respect to lytic replication of EBV,” CD19-positive cells were taken and purified from the peripheral blood of IM patients (Schwarzmann et. al. 124). RT-PCR was used to find characteristic genes of lytic replication. The results found were confirmed using APAAP staining.

It was found that eighty-seven percent of patients expressed the BZLF-1 gene. This is an immediate-early viral gene found at the beginning of the lytic phase. Also the EA group of genes were found in fifty percent of the patients and the VCA group was found in twenty-five percent. EA stands for EBV-induced early antigens and are synthesized

early in the viral replication cycle. VCA stands for viral capsid antigens and are classified as late antigens because expression of the gene is inhibited in the presence of inhibitors of viral DNA synthesis (Epstein, 48). The BZLF-1 findings show that B-Lymphocytes in peripheral blood are permissive to lytic replication in vivo and thus both epithelium and blood cells go through all stages of replication. Therefore there is no difference in the cells with respect to lytic replication. The difference between the findings of the early and late genes may be due to EBV-non-specific immune mechanism.

Epstein-Barr Virus Persists in the Peripheral Blood

After the primary infection, EA genes gradually decrease while the number of EBNA-1 antibodies increases. These antibodies indicate the beginning of infected cell elimination. VCA specific immunoglobulins persist at low levels throughout the life of the host as a result of repeated stimulation of the virus in the saliva. The site of replication and not the infected cell type during IM must be different from that during the latent period because of the different response to the EA antigens. It has been indicated that B-Lymphocytes may be the site where the virus lies latent. So the virus being in the saliva is either due to reactivation of B-Lymphocytes or the virus being gotten through infection. However studies conflict on whether EBV persists in oropharyngeal cells or not.

Consequently, as a proof by contradiction, the next project was to determine if EBV reactivates in B-Lymphocytes of peripheral blood. Again CD-19 positive B-Lymphocytes were taken from patients and purified. However this time, the cells were taken from healthy seropositive individuals. The cells were again assayed using RT-PCR. It was found that in those lacking

evidence of reactivation, ninety percent had evidence of the BZLF-1 gene and none of these patients expressed the EA or VCA group of genes. Still in those patients with evidence for reactivation of the virus, all of them expressed BZLF-1 and EA genes. None of them expressed VCA genes. Thus reactivation correlates with expression of the EA gene. Also replication in the blood only gets to a certain stage, illustrating that the virus is able to replicate in those parts of the body that are not as well patrolled by the immune system as others.

Summary

Lytic replication of the EBV virus is mainly controlled by the host's immune system and cellular factors control replication on an intracellular level.

Works Cited

1. Burkitt's Lymphoma Resources. 24 November 2003. <<http://www.burkitts.org>>
2. Epstein, MA and Achong, B.G., ed. The Epstein-Barr Virus: Recent Advances. New York: John Wiley & Sons, 1986.
3. "Epstein-Barr Virus." Center For Disease Control. 17 November 2003.
4. <<http://www.cdc.gov/ncidod/diseases/ebv.htm>>.
5. "Nasopharynx Cancer." Amersham Health. 24 November 2003. <www.amershamhealth.com/medcyclopaedia>
6. Schlossberg, D., ed. Infectious Mononucleosis. New York: Praeger, 1983.
7. Schwarzamann, et. al. *Epstein-Barr Viral Gene Expression in B-Lymphocytes*. Leukemia and Lymphoma. 30 (1-2): 123-9, 1998 Jun.
8. Roizman, B. , et. al., ed. The Human Herpesviruses. New York: Raven Press, 1993.
9. Winne, Glenna B. *Mononucleosis and Epstein-Barr Virus Infection*. eMedicine. 17 November 2003. <http://www.emedicine.com/ped/topic705.htm>