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Is There A Correlation Between Epstein - Barr Virus (Mononucleosis) and Hodgkin's Lymphoma?

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Abstract

Symptoms of acute Infectious Mononucleosis (IM), which develops after Epstein-Barr virus (EBV) in half the cases, is strikingly like those of Hodgkin's Lymphoma (HL). This, combined with the findings that many patients with HL had a history of EBV and/or IM, triggered an interest in scientists to learn if the two were biochemically related. Many studies in this field unanimously concluded that the development of IM after EBV infection presented a higher risk of developing HL. However, whether this relationship is coincidental or pathological remains a matter of controversy until this day. In the last decade, there has been a lot of research and advances in this field. Various studies have looked at the correlation of EBV and HL considering age factors, genetic predispositions, and immunity and susceptibility dynamics. Researchers discovered that development of HL after EBV was most prevalent in young adults and old patients, pointing to immune system function, or lack thereof. It was also found to be more common in men, suggesting that this may be a sex-related disease. Specific genes activated or mutated in both EBV and HL have proposed that the development of HL after EBV/IM may be genetically regulated. By tracing germinal centre B cell replication patterns, EBV gene expression, and lytic cycle proteins, different mechanisms for the pathogenesis of HL from EBV were proposed. Various studies made use of statistics and patients' medical records to make assumptions. Other methods employed in these studies included probe hybridization to extract DNA and RNA samples from tumor specimens, flow cytometry and polymerase chain reactions (PCR) to identify genetic sequences, and immunohistochemistry to study antigens specific to EBV and related diseases.

Introduction

Is there a correlation between Epstein - Barr virus and Hodgkin's Lymphoma? If so, what is the nature of this relationship? The objective of this paper is to briefly discuss some studies which initially led health professionals to believe that Hodgkin's lymphoma (HL) is caused by EBV. Then, possible causes and mechanisms which may lead the viral disease to transform infected cells to malignant tumors will be expounded upon.

The lymphatic system is an important regulatory mechanism involved in the immune response of the body. It is comprised of lymphatic channels which conduct the lymphatic fluid throughout the body and converge regionally to form discreet lymph nodes (Freeman and Matto, 2018). The function of the lymph node is to evaluate and initiate an immune response when necessary. It functions as an antigen filter consisting of a multi-layered sinus that successively exposes B-cell lymphocytes and T-cell lymphocytes to an afferent extracellular fluid (Evans, 1974). B and T lymphocytes are subtypes of white blood cells that contribute to the immune system. For example, by secreting antibodies, the B cells thus play a central role in immunity. In addition, T cells exhibit cell-mediated immunity. In the course of an immune response, where foreign proteins are recognized and attacked, the immune cell line undergoes multiplication, thereby causing the lymph node to increase in size. Generalized or localized lymphadenopathy, an abnormality in the size or consistency of lymph nodes, is the most common feature in lymphoproliferative disorders. These disorders refer to potentially fatal conditions in which lymphocytes are produced in excessive quantities. Included in this broad category of disorders, are Epstein-Barr Virus, Infectious Mononucleosis, and Hodgkin's Lymphoma.

EBV is a tumorigenic double stranded DNA herpesvirus that commonly develops in the first decade of life of an individual. It infects more than 90% of the human population worldwide

(Yang, et. al., 2015). EBV consists of the EBV-1 and EBV-2 subtypes, with EBV-1 being more prevalent in western societies. An immune response consisting of natural killer (NK) cells and EBV-specific cytotoxic CD8+ T lymphocytes controls the primary infection and reactivation that occurs in all EBV-positive individuals. While EBV is often found in B cells in its latent episomal form, lifelong persistence of EBV in infected individuals involves occasional reactivation to the lytic state, resulting in lyses of infected cells and the release of virus particles which triggers acute infection (Babcock, et. al., 1998).

Primary EBV infections in children are usually asymptomatic yet can result in infectious mononucleosis (IM) development in 50% of adolescent patients (Jenson, 1996). It was not until 1968 that EBV was first associated with IM, followed by further research which ultimately confirmed that EBV was a causative agent of IM. Most of the symptoms of infectious mononucleosis are attributed to the proliferation and activation of T cells in response to infection. It is characterized by abnormally high numbers of circulating CD8+ T cells and B cells. Among its many symptoms, lymphadenopathy and lymphocytosis – abnormal numbers of lymphocytes in the circulating blood (Sawari, et. al., 2016) - acutely resemble HL. In fact, IM is occasionally misdiagnosed as Hodgkin's Lymphoma due to the similarity in their symptoms and small biopsy specimens in the Waldeyer's ring (WR), which may be difficult to differentiate (Delecluse, et. al., 2007). This similarity, among other factors had led researchers to suspect that one disease may derive from the alteration of the other.

According to the World Health Organization (WHO), Hodgkin's lymphoma is a disorder characterized by an abnormality in the lymph node's architecture (Tzankov and Dirnhofner, 2006). HL, also commonly known as Hodgkin Disease (HD), encompasses four histological subtypes, with 40% of sclero-nodular type and 80% of mixed cellularity type carrying the EBV virus (Delecluse, et. al., 2007). It is comprised of characteristic

neoplastic cells known as Hodgkin's Reed-Sternberg (HRS) cells. These interspersed cells only constitute approximately 2% of the total tumor mass while the rest of the tumor consists of T cells, B cells, eosinophils, macrophages, granulocytes, and others (Yang, et. al., 2015). The classic Hodgkin Reed-Sternberg cells are large cells with two or more round nuclei. The mononuclear form is referred to as the Hodgkin cell (Ok, et. al., 2015). HRS cells communicate with other cells via cell contact dependent interactions, including proliferative and anti-apoptotic signals favoring tumor cell survival and expansion. EBV is most commonly associated mixed-cellularity subtype, the most common type of classical Hodgkin disease.

Using data from discharge records of patients hospitalized for Hodgkin's Lymphoma and/or Infectious Mononucleosis, studies were performed by compiling the prevalence of the disorder relating to age and gender. Tracking the medical history of these patients allowed for the determination of how many patients with HL have a past history of EBV/IM. B and T lymphocytes in blood of patients with Hodgkin's disease, infectious mononucleosis, and normal controls were collected and compared. Due to the rarity of EBV-infected B cells in healthy virus carriers, it is complicated to analyze them directly (Caldwell, et. al., 1998). To resolve this issue, Thorley-Lawson developed a method in which human B cells are separated via flow cytometry, which works by suspending cells in a fluid and passing them through an electronic detector. Then, using polymerase chain reaction (PCR), cells are analyzed for the presence of EBV infection. Additionally, using viral DNA and RNA segments from tumor specimens were extracted and studied via southern blot hybridization with probes specific for parts of the EBV genome. Reverse transcriptase of RNA can also be used to identify the genetic sequence of specific genes (Khan, et. al., 1996). Epstein-Barr virus' early RNA transcripts were detected in tumor tissues, via fluorescein-labeled oligonucleotides complementary to the RNA sequence. The fragments were then visualized under a microscope by tetramethyl rhodamine isothiocyanate (TRITC), a bright orange-fluorescent dye. Other studies have applied immunohistochemistry techniques, the detection of antigens in cells of a tissue by introducing antibodies binding specifically to these proteins. Finally, experiments with transgenic mice were useful for studying genes. Control and experimental groups of mice were infected with either wild type (WT) or knockout (KO) genes to see how they affect the course of the disease.

Discussion

It is generally held that a lymph node is considered enlarged when it is larger than 1 cm, however, this can vary depending on the location of the node and the age of the patient (Cheng and O'Connor, 2017). Patients with a diagnosis of EBV, IM, and HD presenting with lymphadenopathy, were studied. The goal was to determine if and how these diseases are correlated. Different propositions as to

the nature of their relationship have been reviewed.

Using data from the Oxford Record Linkage Study (ORLS), a cohort of 2797 patients admitted to the hospital with an International Classification of Diseases (ICD) code for infectious mononucleosis on the discharge record were studied. Patients studied were mostly ages <20-30 at the time of admission. Admission was substantially more common in males than in females. Those with a diagnosis of cancer either before or at the same time as admission for IM were excluded. Tracking the medical records of these patients showed an increased risk for the development of HD with a relatively short follow up period ranging from 1-7 years post discharge (Goldacre, et. al., 2008). A similar study looked at 233 cases of HL in children recorded between 1957 and 2001. Reliable data concerning the onset of symptoms was available in 172 cases, and in 31 of these patients, EBV status was unknown. Of the 141 tumors, 69 (48.9%) were EBV-positive (Reiman, et. al., 2003). In another unrelated cohort study on young adults, it was indicated that individuals who had a history of IM were three times more likely to develop HL (Jarrett, 2003). The incubation period of infectious mononucleosis after EBV was observed to be between 32 and 49 days. (Balfour, et. al., 2015). The follow up period between EBV and HL varied with different genders, ethnic groups, and age.

Both IM and HL typically develops in adolescence and early adult life. In fact, the development of IM after EBV is now considered to be a risk factor for Hodgkin's disease. However, the nature of this association remains unclear. Examining blood samples from patients with HD, showed EBV latency in B cells. However, it must be noted that not all subtypes of HL harbor EBV to the same degree. Some data suggests that the incidence of EBV-positive HL may be age-related. The observed age-incidence pattern suggests that risk of HD is increased among younger people, with a peak in incidence at 25 to 30 years and a second rise after the age of 45 (Khanna, et. al. 1995). An increase in the severity of infection in young patients leads to the development of cancer. In one study, a similar pattern was recorded among aging patients suggesting that the immunologic status of the patient plays a crucial role in the subsequent development of pathologies (Mueller, 1987). Dr. Evans proposed that perhaps HD represent the host's response to an EBV infection that is delayed until adolescence/early adulthood (1974). Another plausible explanation would be that HD develops as a secondary response in patients with genetic susceptibility, low immunity, or a combination of both.

A study was done in which a samples of B and T lymphocytes in patients with HD, IM, and a normal control were analyzed. They then compared the results of each group to the others. In overall counts, the number of T lymphocytes significantly exceeded that of B cells. However, while in infectious mononucleosis the count of T-lymphocytes was elevated, there was a slight reduction in Hodgkin's Disease. It was also observed that in patients with

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HD there was an increase in the number of DNA synthesizing lymphocytes was found when compared to normal controls. The ability of the disease to persist despite potential immune responses against it indicates that the virus has invented pathways to evade the immune system. Also, untreated patients differed from their treated peers in their absolute lymphocyte counts; treated patients presented with a lower number of DNA-synthesizing blood lymphocytes. Cells observed in the blood of patients with Hodgkin's disease and infectious mononucleosis were indistinguishable. Based on these findings, it was inferred that transformed lymphocytes represent normal lymphocytes that have undergone a proliferative response signaled by tumor surface antigens or viral infections (Huber et. al. 1975).

EBV-associated lymphoproliferative disorders (LPDs) are life-threatening diseases commonly found in those with a compromised immune system, especially children. T-cell dysfunction can cause development of mature B-cell lymphoma by impairing immune function. Additionally, a partial lytic infection plays a role in EBV-induced B-cell tumors. Although the main targets of EBV are B cells, EBV may also infect other cells, such as T cells and epithelial cells (Rickinson and Kieff, 2001).

Once infected, EBV persists in rare peripheral blood lymphocytes for the rest of the host's life, usually as a harmless passenger residing in B cells (Ohashi, et. al., 2012). Since there is limited viral protein expression in the latent form, EBV reduces the number of viral proteins that permit the recognition of infected cells by cytotoxic T cells. During its reactivation, which takes place during the lytic life cycle, memory B cells are activated and differentiate into plasma cells. People who have EBV can transmit the disease through oral secretions because the virus replicates in cells in the oropharynx. Generally, the number of infected lymphocytes is stable over time. However, in rare instances, infection of epithelial cells by EBV in vitro results in active replication, and consequently, lysis of the cell which spreads the virus to other cells (Cohen, 2000). Although the primary site of virus replication is in the pharyngeal epithelium, circulating B lymphocytes can become infected too, thereby generalizing the infection. In B cells, persistent infection can transform the cell, which may result in the development of malignant lymphomas, especially Hodgkin lymphoma. Like all herpes viruses, EBV has latent and productive (lytic) phases in its life cycle (Niedobitek, et. al., 2001). Therefore, EBV establishes a life-long infection in individuals which is generally harmless unless the host-virus balance is upset. The latent genes which keep the virus in the host's B lymphocytes induce immortalization and oncogenic potential too. EBV differs from other herpes viruses though in its capacity to transform B cells. Latent infection of B cells by EBV in vitro can result in a transformation to lymphoblastoid cells, thereby leading to immortalization of the cells. In fact, the International Agency for Research on Cancer classified EBV as a group I carcinogen.

In more recent years, studies of tissue cultures of Epstein-Barr

virus growth in peripheral blood lymphocytes has shed some light on the molecular events associated with B cell growth transformation and virus replication (Ohashi, et. al., 2012). Studies have shown that the main type of EBV-associated B-cell lymphoma — that is, Hodgkin lymphoma — seems to derive from germinal-Centre B cells, a structure found in lymphoid tissues that is composed of proliferating B cells. This indicates that EBV-infected germinal-Centre B cells are at the greatest risk for malignant transformation (Küppers, 2003). After B cells are infected, virus-receptor interaction induces activation of the infected cells which enter the mitotic cycle, leading to lymphoblastoid cell lines (LCLs). LCL has the phenotype of an activated B-blast, expressing activation, adhesion, and anti-apoptosis proteins. Since lymphoblasts resemble activated B cells both in their phenotype and molecular features, the virus is thought to push infected naive B cells into the memory state by switching the cell from the growth program to the default program. Normally, the latently infected memory cells shut down the viral expression entering the latent state. However, when the latently infected memory cells divide, they express the EBNA-1 protein causing the viral DNA to replicate. Ultimately, the latent virus is reactivated and proliferates, spreading to other hosts. It is therefore derived that the virus can remain latent in the memory cells for long periods of time without causing any harm to the host. A risk arises if memory cells are accidentally triggered into expressing the growth program (Thorley-Lawson and Gross, 2004).

In germinal centre B cells, a more restricted EBV gene expression pattern is detected in which only EBNA1, LMP1 and LMP2A proteins are expressed (Bancock, et. al., 2000). Also, in the germinal centre expansion causes the number of EBV-infected B cells to increase. These germinal centre B cells then differentiate into memory B cells, which are the long-term latent form of EBV (Bancock, et. al., 1998). In EBV-associated HL, viral genomes were found in their monoclonal form, indicating that infection of the tumor cells occurred prior to their unrestrained replication (Kapatai and Murray, 2007). Therefore, it can be concluded that EBV infects mostly germinal-centre and/or memory B cells, and some naive B cells before they begin to replicate and proliferate (Kurth, 2000). HRS cells are believed to derive from germinal-centre B cells that evaded apoptosis by restricting their own gene expression and by receiving survival signals through stimulation of CD40 (Kanzler, et. al., 1996). EBV-positive malignant cells provide proliferative and anti-apoptotic signals, assisting in survival and growth of the tumor (Kapatai and Murray, 2007). It remains unclear however, under which conditions EBV+ B cells enter germinal centres and how the EBV-gene expression in these cells is regulated, leading to the development of Hodgkin's Lymphoma.

The EBV genome consists of a linear DNA molecule that encodes nearly 100 viral proteins. During the lytic state, these proteins regulate the expression of viral genes causing viral DNA to

replicate. After infecting B cells, the linear EBV genome becomes circular, forming an episome. In these cells, the episome can replicate independently of the host cell, regulated by the cell as part of the normal mechanism of memory B-cell homeostasis, thereby establishing a latent infection (Sarwari, et. al., 2016). The EBV viral genome is encased within a nucleocapsid surrounded by the viral envelope. Entry of EBV into B cells is initiated when the envelope glycoprotein, gp350, binds to the viral receptor on the surface of the B-cell called the CD21 molecule (Kojima, et. al., 2010). Infection of B lymphocytes with EBV results in persistent latent infection and immortalization of the cells to perpetual proliferation.

Studies done using flow cytometry and PCR in biopsy specimens demonstrated reactive B lymphocytes (Kojima, et. al., 2010). Based on these studies, it was observed that EBV infects naive B cells. This was derived from the fact that these are the only cells that were observed expressing all the latent EBV genes. The naive EBV-infected B cells then undergo an expansion phase, thereby making use of normal B-cell differentiation pathways to establish a lifelong persistence in the B-cells. When tracking the primary infection of naive or memory B cells, Latent Membrane Protein 1 (LMP1) and Latent Membrane Protein 2A (LMP2A) were both detected which suggests that they provide the signals for antigen-independent replication in the germinal centre (Macswain and Crawford, 2003). In most HD cases the neoplastic cells are derived from B-cells as indicated by a sequence analysis of the immunoglobulin V region genes revealing mutations. In some cases, nonfunctional genes have been detected by stop codons in their sequence. Another study concluded that the site of persistence of EBV within the body must be the resting memory B cells based on the observation that "shedding of EBV from the oropharynx is abolished in patients treated with acyclovir whereas the number of EBV infected B cells in the circulation remains the same as before treatment" (Cohen, 2000).

In one important study, biopsy specimens of Hodgkin's tumors revealed a 40-50% proportion of EBV positive tumors (Hjalgrim, et. al., 2003). Using southern blot hybridization viral RNAs (referred to as EBERs) and DNA fragments of EBV were detected in 20-25% of specimens. Likewise, patients with Hodgkin's disease were often found to have higher titers of antibody to EBV proteins before or with the onset of lymphoma, suggesting a correlation between the two. Immunohistochemistry was performed on biopsy specimens from patients with HD. Using the immunoperoxidase technique, LMP-1-antibody was applied to the tumor section. Epstein-Barr virus early RNA transcripts (EBERs) were detected in tumor tissues via fluorescein-labeled oligonucleotides complementary to EBER (Alexander, et. al., 2000). The fragment was visualized under a microscope by tetramethyl rhodamine isothiocyanate (TRITC), a bright orange-fluorescent dye.

One study went so far as to suggest that EBV infection is actually the beginning of tumor development. EBV infection

permanently induces B-cell activation, ultimately leading to uncontrollable cell division. EBV-positive HRS cells exhibit a type of virus latency and express different combinations of EBV nuclear and latent membrane proteins. In the first type, only EBNA-1 and EBER are expressed, while in the second, EBNA-1, LMP-1, LMP-2, and EBER are expressed. In the third pattern, all the latency genes are expressed. An additional pattern of latency was found in B cells obtained from the peripheral blood of patients with a past infection of EBV, in which only EBER and LMP-2, and in some cases, EBNA-1 have been detected (Mandage, et. al., 2017). Epstein-Barr virus nuclear antigen 1 (EBNA1) is a protein-encoding gene that is expressed in all EBV malignancies. EBV latent membrane protein 1 (LMP1) is a gene which induces cellular activation and proliferation while inhibiting apoptosis through expression of the B-cell activation markers, CD23 and CD40 (Kapatai and Murray, 2007). EBV latent membrane protein 2 (LMP2A) expression enhances cell survival and inhibits normal B cell transduction. LMP2A does this by mimicking an activated B cell receptor (BCR), replacing the signals that are normally supplied to the B cells and suppresses cell immunity (Caldwell, et. al., 1998). Expression of LMP-2 in transgenic mice allowed B cells to survive even in the absence of normal B-cell-receptor signaling. It was also noticed that during primary infection, many EBV-positive cells appear to express all latent genes associated with viral-driven lymphoproliferative diseases. (Steven, 1997).

BLF1 is a lytic cycle protein found to be involved at both initial and late stages of viral infection. It is involved in DNA replication, repair, and ultimately, immune avoidance. A recent study on EBV BPLF1-knockout mice demonstrated that the BPLF1-knockout mice were approximately 90% less likely to be infectious than wild-type (WT) mice. Without the BPLF1 there was a reduction in transformed human B cells. Overall, humanized mice infected with BPLF1-knockout virus survived longer than mice infected with the WT virus. Additionally, tumors were formed in 100% of mice infected with WT EBV but in only 25% of mice infected with BPLF1-KO virus (Whitehurst, et. al., 2015). These findings suggest that BPLF1 is required for activation of lytic replication and expression. Additionally, ten million cells were injected with either WT or BPLF1-knockout virus and after labeling with B-cell antibody, the total percentage of B-cells in each group was determined using flow cytometry. There was rarely B-cell outgrowth in cells infected with delta BPLF1 virus, suggesting that BPLF1 is necessary for immortalization of B-cells. This provides evidence that BPLF1 plays a role in B-cell transformation, and therefore contributes to EBV's oncogenic role in cells. As of now, the mechanism by which BPLF1 inhibits these processes is still unknown.

Another EBV lytic gene expressed during infection of B cells is BALF1. This gene is known for its anti-apoptotic properties leading to B cell transformations. BARF1 is a secreted protein that blocks Colony Stimulating Factor 1 (CSF-1) signaling, functioning as a trap to block the action of the cytokine. This helps

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the virus evade the host's immune system during acute EBV infection or reactivation of virus from latently infected cells (Ohashi, et. al., 2012).

Since the Epstein-Barr virus is associated with an increasing number of diseases, including infectious mononucleosis and Hodgkin's disease in both immunocompetent and immunocompromised individuals (Yang, et. al., 2015), some research suggests that this correlation may be due to genetic factors. The SH2D1A gene provides instructions for the synthesis of a protein called signaling lymphocyte activation molecule associated protein (SAP). SAP interacts with other proteins to activate signaling pathways that are involved in the control of immune cells. These cells are important in that they help control immune reactions and signal apoptosis. The SH2D1A gene is expressed primarily in T and NK cells as well as in some B-cells (Parolini, et. al., 2002). Therefore, a defective gene causes an alteration of these lymphocytes which most likely results in the inability to control EBV infected cells. To test the possibility of SH2D1A gene involvement in the pathogenesis of Hodgkin's disease, a SH2D1A gene analysis was studied in patients with a history of EBV and EBV-related diseases like Hodgkin's lymphoma. A group of healthy patients was also analyzed to serve as the control group. Results showed an alteration in the 5' region of the SH2D1A gene in the majority of patients with a diagnosis of mononucleosis, of which 25% went on to develop malignant B cell lymphomas. This indicates that there may be a genetic correlation between EBV and HL.

The SH2D1A gene is located on the X-chromosome, which may contribute to the fact that males are more prone to develop Hodgkin's Lymphoma after EBV (Robinson, 1976). Unlike females, males do not have another X chromosome to counteract the mutated gene. In one study 23 patients with HD, consisting primarily of males, had their X-chromosomes analyzed. Analysis by reverse transcriptase polymerase chain reaction (RT-PCR) found EBV genome or protein in 16 of 23 tumor samples. The risk of contracting Hodgkin's disease was found to be significantly increased in males who had a positive reaction to the Paul-Bunnell test, a heterophile antibody test that screens for IM. (Rosdahl, et. al., 1974). Notably, anti-EBNA-1 antibody levels showed 43% heritability.

In a study on transgenic mice, EBNA1 and LMP1 proved to play a key role in lymphoma development. EBNA1 is essential during cell division ensuring equal partitioning of a cell, while contributing to immortalization of cells by allowing for the maintenance of newly synthesized plasmids. The central part of EBNA1 consists of Gly-Ala repeats, which are believed to block the processing of proteins by proteasomes. This functions in inhibiting immune recognition and apoptosis of infected cells because viral proteins are normally broken down by proteasomes to peptides for recognition by cytotoxic T cells (Kojima, et. al., 2010). In turn, the infected cells that accumulate have oncogenic potential. During recovery

from the acute phase, CD8+ T cells return to normal levels and antibodies develop against EBV nuclear antigen-1 (Balfour, et. al., 2015). LMP-1 mimics CD40 and activates the nuclear factor-kappa B, promoting cellular proliferation (Ok, et. al., 2015). LMP-1 also induces BCL-2 and cyclin-dependent kinase 2, activating cell replication and inhibiting cell death.

Conclusion

Although an association has been identified, the pathogenetic role of EBV in these diseases is still unclear (Flavell, et. al., 2000). Likewise, the exact factors responsible for cancer development remains a matter of debate. Researchers are limited in their investigation of the relationship between viral infection and the development of cancer due to the lack of small animal models that can accurately reproduce the biology of EBV. Yet over the past few years, some important advances have been made in understanding the biology of EBV and its role in the development of EBV-associated lymphomas. The observation that a significant proportion of cases of HL contain the Epstein-Barr virus genome strongly suggests that the virus contributes to the development of the lymphoma. Significant progress has been made in understanding the functions of EBV-encoded genes in B cells (Sarwari, et. al., 2016) and viral protein functions. Several key issues remain to be clarified.

Additionally, whereas EBV infection in tumors has been firmly established by several independent research groups, its association remains controversial. Many still believe that it is by coincidence, mainly due to the fact that the origin of Hodgkin's can be regarded as heterogeneous because only half of the cases are known to be associated with EBV (Tamayose, et. al., 2004). Others maintain that Hodgkin lymphoma is a multi-factorial disease which depends on both biological and environmental factors and therefore, a specific causative agent cannot be pinpointed (Huang, et. al., 2012).

There is no current approved treatment for EBV. Ongoing research is currently trying to develop vaccines to prevent or treat these conditions. This is a difficult task due to a lack of an animal model to study the pathogenesis of the disease. It is further complicated by the fact that the number of virus-infected cells in the body would amplify and establish latency before immune mechanisms develop. A future approach would be to synthesize therapeutic vaccines designed to generate specific immune attacks for the latent virus. Adoptive immunotherapy and EBV-specific pharmacologic therapies offer promise for future treatment.

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