Role of Epstein-Barr viral genes in lytic and latent states

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Abstract: Epstein-Barr virus (EBV) is world widely distributed. About 98% of adults are infected with EBV. Early childhood is shown to be infected with EBV, EBV possesses many proteins having sequence and functional homology with many human proteins. EBV open reading frames such as BRLF1, BRCF1, BARF1, BHRF1 and BILF1 program the host for lytic and latent states as well as acute and chronic infections. EBV can induce production of some cytokines such as IL-15 (with TNF-α), IL-10, and IL-6. On conclusion, much organized efforts in the future studies are needed for EBV to be controlled as with the time pass, our bodies will become saturated with this virus. our recommendations are retrospective identification of the previously discovered viruses with electron microscopy, followed by whole genome sequencing, sequencing of whole glycoprotein B gene for any suspected herpesvirus, extensive studies for autoimmune antibodies to know if they are idiopathic or for enveloped EBV or its components and finally considering feces one of the modes for infection.
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Introduction:

Epstein Barr virus (EBV) is world widely distributed (1) and about 98% of adults are infected with EBV (2). Early childhood is shown to be infected with EBV as well (3).

Genes of EBV and interleukins induction:

EBV possesses many proteins having sequence and functional homology with many human proteins. BRLF1 is used by the virus during viral episomes latent replication by tethering its copies with the host chromosomes during mitosis in the dividing cells (4). BCRF1 and BARF1 open reading frames code for proteins for evading the immune response during the acute infection of EBV or the viral reactivation in latently infected cells through inhibition of alpha (α) and gamma (γ) interferons which inhibit the growth of infected cells with EBV (5). EBV also possesses a homologue of cellular interleukin (IL) 10 which is encoded by BCRF1 (6). IL-10 was known to be a stimulator for the proliferation of mast cells, and this may explain the cases of hypersensitivity. In addition to two homologues of B cells lymphoma-2 (BCL-2) encoded by BHRF1 and BALF1 genes which have significant roles in cell immortalization mechanism by apoptosis inhibition (7).

EBV is a γ-herpesvirus and it has the property of encoding seven-transmembrane receptors with structural and functional homologies to receptors of the host which are known as G protein-coupled receptors (GPCRs) that have a seven-membrane domain to play a predominant role for transducing signals from outside to inside cells where γ-herpes viral GPCRs show many functions, including scavenging of the host chemokines in addition to cell-to-cell adhesion and reprogramming for the intracellular signaling net for promoting efficient replication of the virus as well. BILF1 is an important EBV open reading frame (8). This gene is expressed during the lytic cycle of EBV and was identified as a strong viral GPCR. BILF1 is examined to have a function in the situation of immune evasive effect. It is considered a highly tumorigenic agent for both, in-vitro and in-vivo (9). i.e., it is an essential EBV gene for mediation of immunosuppression and oncogenesis (10).

EBV can induce production of IL-15 and tissue necrosis factor-α (TNF-α) (11) to maintain and stimulate cytotoxic T cells proliferation resulting in tissue damage (11)(12) without indiscrimination for auto-destruction of host tissues (13), and viral by product and cell debris that results may be misdiagnosed as bacilli or spirochetes. This process explains how EBV can cause over-activation of T cells in addition to macrophages to result in the over-production of cytokines giving fatal coagulopathy with or without myelinolysis as a serious condition (14).

Micro RNAs of EBV:

EBV viral micro RNAs are another important factor that can suppress target genes in EBV as well as host genes to maintain a latent infection for EBV. EB viral micro RNAs evade the host immune surveillance system and promote tumorigenic growth for infected cells (15). Micro RNAs were used by EBV for switching between lytic and latent infection to maintain EBV infection and evade its recognition by the immune system of the host by reducing the expression of the viral (antigenic) gene. Moreover, micro RNAs target genes that are involved in host immunity by suppressing them. EBV exploits micro RNAs for malignancy transformation. Also, secreted exosomes from B lymphocytes which are infected with EBV were found to contain a huge amount of host and viral micro RNAs transferred to epithelial cells. So, derived micro RNAs from cells infected with EBV can affect the infected and non-infected host cells (16).

EBV TATA boxes:

EBV possesses TATA boxes as all the promoters were shown to have sequences of about 30 bases which are found upstream of transcription starts for them that were homologous with the TATA AAA sequence (17).

Actions of IL-6:

IL-6 is severely elevated in both cases of EBV infection, acute and chronic in patients with symptoms (18). It acts as an essential corticotropin-releasing hormone-independent stimulator for the adrenal axis during the activation of the immune system (19).

IL-6 induces the production of serum amyloid A (SAA), fibrinogen, haptoglobin and α1-antichymotrypsin (20). SAA leads to cytomegalic and syncytia formation because of the fusion of the EBV infected cells detected in histopathology in severe infection. Fibrinogen leads to thrombosis and increases the viscosity of blood. α1-antichymotrypsin leads to failure in destroying phlegm and fibrinous inflammation. Haptoglobin leads to tissue damage or dysfunction resulting from the oxidative stress of free hemoglobin.

Magnesium levels in serum are found to be associated with elevated IL-6 levels. Magnesium is known to be essential for cell growth regulation, differentiation, division, synthesis of proteins, cell signaling in addition to structural functions to an extent that adding magnesium to potable water reduces the risk for cancers of the liver, esophagus, breast, prostate, and ovaries (21). Also, low levels of plasma cyanocobalamin (Vitamin B12) were shown to be associated with excessive production of IL-6 (22).

Ovarian cancer G-protein coupled receptor stimulates IL-6 which causes epithelial fibrosis in addition to collagen deposition, mast cell proliferation, peripheral tolerance inhibition as well as hypersecretion of mucous from airway epithelial cells (23).

Pathological conditions related to EBV:

EBV research wasn't explained enough in the previous years and was neglected depending on references mentioned that EBV infections are mostly mild and asymptomatic although it was the first virus known to be linked to human cancers more than 50 years ago (24), shown to be linked to autoimmune diseases (25), vasculitis (26), organ failure (11), myocarditis (27), thrombosis (28), cytokine storm syndromes (18), smell, taste and hearing distortion (29), other many serious diseases (30), fetal anomalies (31), and abortion (32).

A lot of studies need to be extensively reexamined. For example, autoantibodies such as anti-red blood cells antibodies trigger phagocytosis of red cells by activated macrophages in experimentally infected rabbits with EBV which presented hemophagocytic syndrome (33). Are these antibodies being idiopathic, or they are for enveloped EBV and/or for its components (capsids, proteins, double-stranded DNA) that react with the virus and/or its components in different tissues? So, misdiagnosis may result in some conditions as in the case of mycobacteria (leprosy and tuberculosis) where autoantibodies were detected (34). These autoantibodies may be due to enveloped EBV or its components.

EBV mainly infects B cells through CD21 receptor and CD21-negative T cells, natural killer cells and epithelial cells (35). EBV infects 1 in 100 to 1000 B lymphocytes during acute infection and clinical disease. On the other hand, it infects 1 in million B lymphocytes during latency (36). However, EBV possesses growth-transforming activity for human B cells (37).

EBV in adult and childhood:

When the liver becomes injured, CD8+ lymphocytes increase rapidly in the liver. This explains that about 85% of patients infected by EBV have impairment in the liver function of different degrees (38). EBV infection can induce cholestatic hepatitis among the pediatric population (39). Chronic active EBV infection which is considered a lymphoproliferative disorder occurs mainly in children (5), in addition to central nervous system vasculitis, resulting from EBV associated T and

natural killer cells lymphoproliferative disease (26). Hypersensitivity to mosquito bites which is associated with chronic infection of EBV in addition to natural killer cells lymphocytosis are detected among children (40)(41). This explains the studies mentioned before stating that acute malaria infection increases circulating levels of EBV which is cleared after anti-malaria treatment (42)(43). But it's heavily thought that mosquitos can independently transmit EBV whereas vectors including insects could transmit a gamma-herpesvirus called ovine herpesvirus 2 (OvHV-2) which surprisingly has similar genes to EBV and host, shared symptoms, gross pathology, and histopathology with EBV infection such as vasculitis, thrombosis, infiltration of tissues with lymphocytes and macrophages in addition to susceptibility of all organs for infection (44), and factors affecting the rate of incidence including climatic factors, presence of vectors and stress levels as well (45).

Conflictions related to previous studies:

Previous studies might conflict with the pathophysiology of the disease. For example, Marek's disease is known to be caused by herpes viral infection. Some authors classify it as gamma-herpesvirus (46), but other authors identify it as alpha-herpesvirus. Some studies mentioned that sheep are carrier only for OvHV-2 infection without symptoms, however other studies denote the presence of symptoms in sheep (44). Other studies mentioned that lambs do not become infected before 3 months with OvHV-2. On the other hand, recent studies mentioned that lambs can be infected rapidly following birth through horizontal transmission with OvHV-2 (47) which is the major cause of malignant catarrhal fever (MCF) within ruminants in zoos and wildlife parks (48), not to forget to mention that feces is the new mode of transmission for OvHV-2 (48).

Conclusion and Recommendation:

In conclusion, much organized efforts in the future studies are needed for EBV to be controlled as with time pass, our bodies will become saturated with this virus. Our recommendations are Retrospective detection of the previously discovered viruses by electron microscopy (EM) to know the viral family and next generation sequencing for DNA and RNA of the viruses because previously discovered RNA viruses such as influenza, HIV, HCV, Zika...etc, may be messenger RNAs of EBV proteins depending on symptoms. Sequencing of whole glycoprotein B gene for EBV and OvHV-2 or any suspected herpesvirus. Sequencing of different genes of EBV or OvHV-2, their messenger RNA and their coupled proteins. On observing electron microscopical examination for MERS, SARS or for COVID-19 and its variants by negative staining and thin section techniques, they were for a herpesvirus, so retrospective studies for previously diagnosed cases for COVID-19 or its variants using EM, gross pathology, histopathology, hematology, biochemistry, and molecular biology for EBV or OvHV-2 is recommended, taking in consideration that EM of EBV (OvHV-2) is characterized by the presence of enveloped virus, capsids, proteins of different sizes and double stranded DNA. Extensive studies on the autoimmune antibodies to know if they are idiopathic or specific for enveloped EBV or its components (capsids, proteins or dsDNA) in blood and different tissues. Studies for antibodies on large scale and try to know if persons have no EBV antibodies took intrauterine infection with EBV before their immune system development in infantile stage (non-self). Taking in consideration that feces is one of the modes of infection for EBV. Seeing the possibility of the presence of EB viral genome tethered to human genome and if there is association between site for tethering and form of the disease.

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