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Review Article

Humoral and Cellular Immune Response against Epstein Barr Virus Associated with Lymphoproliferative Malignancies

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Abstract

One of the 8 known human herpes viruses is Epstein-Barr virus. Over 90% of human population in the world are infected by the virus. It's recognized as having significant role in the development of cancers derived from lymphocytes and epithelial cells. It causes infectious mononucleosis in primary infection and also causes several lymphoid and epithelial malignancies, including Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, nasal T/NK lymphomas and gastric cancer.

Host immune responses have a great role in both controlling the lifelong virus carrier state and also preventing the primary infection. In healthy individuals and in normal circumstances, EBV infections are generally controlled by the immune system through the action of antigen-specific T lymphocytes.

The virus can be spread and persist in human if there is a disruption in the human immune system due to the evasion of the virus. EBV infections are controlled by multiple levels of host defenses, normally described as innate and adaptive immune responses. The innate immune response can be divided into cellular and humoral components generated by recognition of molecular pattern.

The objective of this review is to forward current knowledge regarding the human immune response against the virus and apply those mechanisms for tumerogesis in different immune cells. The review was compressive research articles from PubMed and Google scholar selected by using key words related to the title.

Keywords: *Epstein-Barr Virus; Cellular Immune Responses; Humoral Immune Response*

Introduction

Epstein-Barr virus (EBV) is a double-stranded Deoxyribonucleic acid (DNA) virus that is categorized under the family of Herpesviridae and subfamily of Gamma Herpesviridae. EBV is a γ-1 virus that infects B-lymphocytes and has the ability to convert B-lymphocytes after latent infection in the host. The virus was initially identified by Epstein's group in 1964 from Burkitt lymphoma patient cell line [1]. Since EBV is ubiquitous, it infects greater than 90% of the world's population [2].

EBV associated cancers are those in which EBV DNA, ribonucleic acid (RNA) and/or viral gene expression can be detected in the malignant tissues. These diseases include Hodgkin's disease (HD), post-transplant lymphoproliferative disorders (PTLD) and Burkitt's

lymphoma (BL). Although EBV is a B-lymphotropic virus, it has been detected in T-cell lymphomas, nasopharyngeal carcinoma (NPC), oral hairy leukoplakia (OHL), and gastric cancer and can infect T lymphocytes or epithelial cells (GC) [3,4].

EBV infects lymphoid and epithelial cells through different attachment and entry mechanisms. The virus goes through a lytic replication cycle in both cell types, resulting in the creation of infectious viruses. The lytic replication of EBV in B cells is frequently occurred after the reactivation of latent virus while in epithelial cells it has been showed to occur directly in primary infection after viral entry to the cell [5].

The immune system protects its host by recognizing and opposing intruders; the frequency and severity of EBV-related disorders, particularly in immunocompromised patients, underscore the crucial role of immunological responses in regulating this virus infection. Understanding the role of the host's immune responses in EBV infection would help researchers better understand how EBV can persist in the infected host and drive cell transformation [6].

In immune-competent hosts, the development of EBV immortalized B cells is prevented by a rapid increase of EBV-specific memory T cells directed against both latent and lytic antigens [7]. Individuals with immunological deficits, whether inherited or acquired, or who are EBV positive, are particularly vulnerable to viral reactivation and cancer transformation. In addition, in EBV-sero positive patients following organ/stem cell transplantation and treated with Immunosuppressive medications are at higher risk for PTLD development [8].

EBV is a major human viral pathogen with a poorly understood immune evasion mechanism. An improved understanding of the molecular and immunological mechanisms of EBV leading to the development of these malignancies, may help us to come up with better prognostic, treatment and management regimens in the future. Therefore, this review will give for readers about how our immune system tries to fight against the virus and apply those mechanisms for tumerogesis in different immune cells. It will also show the mechanisms in which the use of immune cells to eliminate the virus through immunotherapy.

EBV associated lymphoproliferative disorders

EBV infects the majority of the world's adult population, and once infected, these people carry the virus for the rest of their lives. In developing nations, primary infection with the virus occurs often during the first few months to years of life and is generally asymptomatic Infectious mononucleosis patients' oropharyngeal secretions, immunosuppressed patients' oropharyngeal secretions, and healthy EBV sero-positive persons' oropharyngeal secretions all contain the virus's infectious form [9].

When we say EBV associated malignancies, it refers to disorders in which viral genome or gene products were detected within cancerous cells, although in theory the virus may encourage the changes associated with malignant transformation so far it could also be lost from the tumor cells [10]. Depending on tumor type, the mechanism of tumor causation by EBV differs. However, some viral basic general characteristics are found in the several EBV-associated malignancies. Establishment of a persistent infection is the first stage in the mechanisms of EBV tumorigenesis [11]. EBV also infects the squamous epithelium of the oropharynx and nasopharynx, smooth muscle cells, follicular dendritic cells, and glandular epithelium of the stomach, thyroid, and salivary glands. Most EBV-associated illnesses are derived from EBV-infected B lymphocytes, which are the main cellular reservoir for EBV persistence [12].

The role of EBV in the pathogenesis of a variety of lymphoid and epithelial malignancies is recognized. The virus has a strong growth-transforming property Immunodeficient individuals, such as HIV-positive patients and those with other hereditary immunodeficiencies, those taking immunosuppressive drugs after transplant, and persistent active EBV infection enhances the risk of causing EBV-associated cancers [13].

The lifecycle of the virus starts from oropharyngeal or nasopharyngeal mucosa and primary EBV infection undergoes its first lytic replication in this area. The virus then establishes latent infection by spreading to the submucosal lymphoid tissues where it infects naïve B

and cells. A latency III pattern is observed in infected naïve B cells; where all the latent genes are present, making the virus-infected cells vulnerable for removal by the cytotoxic T-cell immune response. To escape immune surveillance, EBV down-regulates antigen expression and drives the infected B cell to further differentiate. A latency II pattern can be found in the germinal center where EBV nuclear antigens and latent member proteins (EBNA1, LMP1, LMP2A, and LMP2B) are present. These proteins enable the infected B-cell to survive, further differentiate into a memory B cell and enter the memory B-cell reservoir. In the memory B cells, nearly all the EBV protein expression is switched off (latency I/ latency 0) [14].

Different types of lymphomas are associated with different patterns of latency programs. The type I latency type that expresses only EBNA 1 is observed in Burkitt's lymphoma patients. Whereas latency type II is known by the expression of EBNA-1, LMP-1 and LMP-2 is seen in Hodgkin's lymphoma and peripheral T-cell lymphoma cases. Latency type III, also known as the "growth program," express all the nine latent-cycle EBV antigens and commonly found in post-transplantation lymphoproliferative disorders [15].

Immune response for EBV associated lymphoproliferative disorders

Immune responses of the host are thought to have a central role in both limiting the primary infection and controlling the lifelong EBV carrier state. EBV infections are not life-threatening and are generally effectively controlled by the immune system through the action of antigen-specific T lymphocytes in healthy individuals and under normal circumstances. The viral infection in humans' results in responses of both cellular immunity and humoral immunity against the EBV virus. Almost all patients with EBV- associated malignancies are EBV seropositive. In most viral infections, an early-onset of IgM response is the characteristics of EBV exposure [16].

Cellular innate immune responses

Oropharyngeal epithelial cells and B cells are the principal targets of Epstein Barr viruses, with the oropharyngeal epithelium serving as the initial innate barrier to infection. From cell surface, endosomal, and intracellular sensors to IFN synthesis and signaling, these defenses and responses can occur along a variety of paths and phases. This interaction between the virus and innate immunity is important for the outcome of infection to be occurring [17].

The mystery of how EBV makes contact with B cells through the epithelial barrier remains unsolved, and no definitive answer has been found. EBV released from B cells is epithelial cell tropic, whereas EBV released from epithelial cells is B-cell tropic, according to one current model [18].

EBV predominantly enhances the innate immune response in initial infection by the activation of Toll-like receptors. Pattern recognition receptors in the host identifies the virus elements which then activates the immune system's natural antiviral defenses against EBV. The creation and release of cytokines such as tumor necrosis factor, interleukins and interferons by infected cells is the result of this innate immune response. One of the host cells' most important antiviral defensive mechanisms is the type I interferon response [19].

During primary EBV acquisition, innate immune responses mediated by NK and NKT cells could be involved. The function of NK cells is either defense against the viral infection or pathogenesis of IM [20]. Additionally, NK cells can also prevent B cells from being transformed by EBV [21]. To avoid innate immune detection and the activation of antiviral mechanisms, EBV acquired a number of efficient defense responses [22].

Humoral innate immune responses

The different particles in EBV can be detected by a number of PRRs. TLRs can sense viral particles on the cell surface as well as in endosomes. RNA and DNA sensors, as well as inflammasomes in the cytosol, can detect viral-derived components. TLRs, RNA, and DNA sen-

sors trigger a cascade of intracellular signaling events that activate NF-B and interferon-regulatory factors, resulting in gene transcription and the creation of type I interferons and cytokines. Through signal transducer and activator of transcription molecules, surface cytokine receptors recognize the secreted cytokines. Currently, latent and/or lytic EBV proteins, as well as EBV miRNAs, target several phases in these PRR signaling pathways [16].

EBV infection and production of several lytic EBV gene proteins can limit the secretion of multiple antiviral cytokines. Interferon response genes and type I interferon production are inhibited by the two immediate early lytic proteins of EBV (BZLF1 and BRLF1) [23]. The lytic EBV proteins may potentially affect the human natural defense by modulating TLR expression and interfering with intracellular NF-kB activation on the surface of virally infected cells [24].

Cellular adaptive immune responses

In order to control EBV during both the initial and chronic phases requires cellular immunity. EBV-infected or EBV-transformed B cells can be differentiated through both $CD8^+$ and $CD4^+$ T lymphocytes and they are able to inhibit the growth of the malignant cell. Major Histocompatibility Complex (MHC) that are expressed on the surface of infected or transformed B lymphocytes are needed for EBV-specific T lymphocytes to recognize antigens as molecular complexes formed by viral peptide epitopes [25,26].

The primary role of $CD8^+$ and $CD4^+$ T cells in the cellular immune control of EBV latency I and II malignancies might be to lyse targets presenting EBNA1 and/or LMP1 on MHC. However, against EBV latency III it is likely that $CD4^+$ T cells play an essential role in helping $CD8^+$ T cell responses that targets the EBNA3 and LMP2 proteins. LMP1 is poorly recognized by $CD8^+$ T cells, but targeted frequently by $CD4^+$ T cells [27].

CD8 T cell responses are aimed at a number of epitopes found in latent cycle antigens. Latently infected HLA class II-positive target cells can be recognized by a subset of these CD4 responses against particular epitopes [28]. Resistance to EBV-transformed cells by EBNA1-specific $CD4^+$ T cells could be occurred through their cytokines and lytic function or by sustaining the $CD8^+$ CTL response to other lymphoma-related EBV products such as LMP1 and LMP2 [29].

Humoral adaptive immune responses

The virus stimulates a humoral response with particularly strong responses to some of the lytic cycle proteins. Many people with initial EBV infection have robust IgM and evolving IgG responses to different viral proteins. IgG responses to certain of the early lytic cycle proteins, often known as early antigens, as well as the latent protein EBNA 2 are generally detected. Neutralizing antibodies are also produced against a component of the membrane antigen (gp350) and occur somewhat late during the course of primary infection. Therefore, they are unlikely to play an important role during the early phase of the infection in preventing the spread of virus [26].

The evaluation of the humoral response to EBV is primarily motivated by its diagnostic potential and the production of EBV vaccines. Antibodies produced for the response to the viral capsid antigen first emerge during natural infection and may play a key role in neutralization of the virus. VCA is expressed recently in the lytic phase of infection, and it most likely follows earlier T cell responses to immediate early and certain early antigens in terms of the adaptive immune response's evolution. IgM antibodies to viral structural proteins indicate primary, acute infections, whereas IgG antibodies to VCA that develop later and might last a lifetime may signal a recent infection or a previous infection. Antibodies to EBNA, a latent cycle protein that can persist for years after infection, indicate a previous infection, whereas EA-D IgG can indicate viral reactivation. As a result, determining the overall serostatus of these multiple antigens is critical in determining whether the individual has an early, primary infection, an ongoing active infection, a past infection, or even viral reactivation [30].

Viral strategies against immune evasion

Immune evasion is one of the characteristic features of human malignant cells. External antigens produced in virally infected cells are the targets for immune discovery. EBV has multiple strategies to evade host immune destruction and cause infections. The diverse activities of EBV lytic proteins after lytic reactivation of EBV in B cells functioning on immunological evasions are well known [23].

EBV immune evasion techniques have been implicated to both lytic and latent cycle gene products, and also to miRNAs encoded by the virus. Infected cells interfering with antigen presentation, molecule production that reduce natural or adaptive immune cell function, inhibition of the production of antiviral proteins, and inhibition and modulation of the cell death pathways used by virus-specific effector T cells or NK cells are all possible effects of these gene products and miRNAs [31].

The modulations of host immune responses are taken place by the latent EBV gene products and play an important role. By interacting to PKR, a double-stranded RNA dependent protein kinase, EBER, an EBV-encoded gene product that is produced at high levels in all latency phases of the viral infection, can suppress interferon-stimulated gene activity [32]. EBV has utilized a number of strategies to avoid infected cells from apoptosis in order to increase viral persistence. Binding to the pro-apoptotic protein Bim via a functional bcl-2 homolog encoded by BHRF1 triggered by a variety of stressors can decrease apoptosis [33].

Concluding Remarks

Epstein Barr Virus shows that it uses a wide range of evasion mechanisms to modulate innate and adaptive immunity during its life cycle. These evasion strategies are likely to contribute to the occurrence of EBV-associated cancer. A deep understanding of the strategies of EBV in immune invasion will help in the development of novel strategies to combat infections caused by EBV and its associated malignancies [33].

Many EBV-encoded proteins have been discovered that disrupt host immune responses in both the latent and lytic phases of the infection. Evasion strategies of the virus by exploiting and counteracting, sensing of EBV and innate immune recognition still need much further work to understand the mechanisms and underlying causal relations [34].

To understand the role of $CD8^+$ T cell response to EBV, many advances have been made and progress has been made in understanding $CD4^+$ T cell immunity more recently. There are challenges in using these information that may be used to prevent and treat EBV-associated disease by developing vaccines and other forms of immunotherapy [26]. A serious and unresolved challenge to develop a viral targeted therapy is a challenge of targeted delivery of EBV-dependent vectors specifically to the tumor cells [35].

In conclusion, EBV used a number of ways to promote viral infection and perseverance in healthy people. The virus, the host B cell, and the immune response begin a complicated, continuing relationship when the virus infects them. Disruption of host immunity or dysregulation of these pathways, on the other hand, may play a role in the development of EBV-related malignancies. In order to comprehend the outcome of EBV infection, more research is needed to define the processes by which EBV affects B cell function, the immunological response to EBV, and the significance of viral variety. There should be more exploration to fully realize the complications related to EBV-driven malignancies and their immune responses [36].

Conflict of Interest

The author has no competing interest.

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