

## Epstein-Barr Virus and Malaria Interactions: Immunology Perspective

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### ABSTRACT

Epstein-Barr Virus can cause various diseases, from acute inflammatory diseases such as fatal or chronic EBV infection, infectious mononucleosis as well as lymphoid and epithelial cancer, various autoimmune diseases, and also could interact with malaria. As EBV infects 95% of the world population, and more than 30% are infected with the protozoan parasite, with more than 500,000 deaths due to malaria cases. It is important to understand how EBV dysregulates the immune system, especially when the virus is interacting with other pathogens such as malaria parasites, causing more severe conditions in certain people like Burkitt Lymphoma. This review will be informative about the mechanism of how EBV interacts with malaria parasites and how it affects the immune system. Knowledge of various cytokines triggering the immune system which may provide links to control/minimize malaria disease severity.

## 1. Introduction

From the previous research, it was confirmed that malaria and EBV has a strong correlation starting from the research findings of (Piriou *et al.* 2012; Wilmore *et al.* 2015), which discovered that malaria patients, including children and pregnant women, have increased EBV-DNA loads in their plasma compared with those with negative malaria, suggesting that EBV could be reactivated during malaria infection. There is a direct correlation of an increase in plasma EBV viral load proved by the progression of endemic Burkitt Lymphoma, which is also followed by the increase of *P. falciparum* antibody titers (Asito *et al.* 2011; Graham and Lynch 2020). Another discovery found that increased circulating EBV viral load is also associated with increased exposure to *P. falciparum* malaria, which contributed directly to the severity and malaria disease stages, suggesting that *P. falciparum* infection promotes reactivating viral replication (Daud *et al.* 2015; Rasti *et al.* 2005). Based on the background that has been described above, this review article is to understand better the interaction of Epstein-Barr Virus (EBV) and malaria parasites

and how the immune system works in complexity on facing these two pathogens.

## 2. Epstein-Barr Virus (EBV)

Epstein-Barr Virus (EBV) is one of the most widespread viruses that infect humans. EBV infection continues for life after primary contact, and the virus has spread throughout the world in about 95% of all humans. EBV infects epithelial cells and B cells (Ali *et al.* 2015). The B cells stimulated and transformed by the virus and the epithelial cells permit complete lytic replication (Ali *et al.* 2015; Hadinoto *et al.* 2009; Tsao *et al.* 2012). The virus infects cell types that express the receptor CR2 or CD21, such as pharynx cells (Birkenbach *et al.* 1992; Jiang *et al.* 2008; Smith *et al.* 2020). The pharynx cells contain few unintegrated copies (episomes) of the virus genome, which are replicated every time B cell divides (Roughan *et al.* 2010). From these EBV producing plasma B-cells EBV can be transferred to local (oropharyngeal) epithelial cells where replication is increased and the virus is shed into saliva (Hadinoto *et al.* 2009; Tsang *et al.* 2014). EBV is transmitted most commonly in saliva as well as blood, the infection is usually latent, "sleeping" and often asymptomatic, but EBV can be triggered to cause severe diseases, including cancer

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(Odumade *et al.* 2011; Shannon-Lowe *et al.* 2009). EBV is able to manipulate host gene expression by providing various signals to influence molecular control pathways that are important for normal B cell function (Thorley-Lawson and Allday 2008). A number of EBV gene products offer benefits for B cell survival and transform oncogenic host cells or permit the existence of clones that are normally prohibited (Wu *et al.* 2014).

Abnormal viral activity is reflected in a distorted humoral immune response, which can be measured in vitro using patient samples (blood, saliva or serum/plasma). Usually, EBV infection does not cause health problems, but in certain people, EBV can cause various diseases such as Infectious Mononucleosis (IM), Nasopharyngeal Carcinoma (NPC), Hodgkin's Lymphoma (HL), Multiple Sclerosis (MS), Oral Hairy Leukoplakia (OHL), Inflammatory Bowel Disease (IBD), Gastric Cancer, Burkitt Lymphoma (BL) and others (Kutok and Wang 2006; Kuri *et al.* 2020; Taylor *et al.* 2015) and also involves interaction with environmental agents, including malaria. EBV infected B-cells can interact with the malaria parasite, *Plasmodium falciparum*, which may lead to endemic Burkitt Lymphoma (BL) (Moormann and Bailey 2020). The pathogenesis of BL involves an association between EBV and malaria caused by *P. falciparum* is the most common cancer in sub-Sahara children and Papua New Guinea (Asito *et al.* 2011; Lavu *et al.* 2005; Thorley-Lawson *et al.* 2016).

### 3. Malaria

Malaria is a parasitic infectious disease caused by infected mosquito Plasmodium parasite and spreads as a serious tropical disease country (Snow and Omumbo 2006). Recognize as an easily transmitted disease and cause severe symptoms such as severe anemia, kidney failure, and death if not treated properly (White 2018). Malaria is transmitted by female Anopheles mosquito (Cox 2010) causes the parasites to enter the human body and reside in the host's liver cells to do proliferating before it is ready to attack red blood cells and starting the symptoms to appears (Posfai *et al.* 2018). Sporozoites are discharged from mosquitoes which attack hepatocytes and duplicate into merozoites. Merozoites released from hepatocytes will then enter the circulation of blood within the human body and infect erythrocytes or red blood cells. Erythrocytes at that moment undergo

destruction when parasites break down the amino acid from hemoglobin (Hay *et al.* 2010; van Tong *et al.* 2017). Each of the plasmodium types will show different symptoms that trigger serious complications such as brain damage and multiple organ failure. These complications are more vulnerable to children under five and the elderly (Posfai *et al.* 2018). *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* are five species of plasmodium protozoa that transmit diseases to people. In malaria-endemic ranges, *P. falciparum* is the foremost broad and most harmful. In 2010, nearly 200 million cases of malaria around the world, and an assessed 650,000 deaths, of which 91% (596,000) were reported from Africa (van Tong *et al.* 2017; WHO 2014).

### 4. Immune System

The immune system will identify pathogenic infections in 2 types of responses, specifically the innate and antigen-specific adaptive immune responses (Marshall *et al.* 2018). The innate immune response is the primary protection that arises rapidly, involves leukocytes such as neutrophils, monocytes, macrophages, eosinophils, mast cells, dendritic cells, etc. At the same time, the antigen-specific adaptive immune response covers long-term defense and is activated when specific T cells identify the antigen that has been displayed by the antigen-presenting cell (Rivera *et al.* 2016). Both the innate immune response and the antigen-specific adaptive immune response will stimulate many immune cells to produce different cytokines family. These cytokines will lead their differentiation to and suppress or promote the immune response. This activity of immune response is critical for infectious pathogen clearance (Muñoz-Carrillo *et al.* 2018).

The immune system is a very orderly and balanced system, but when the balance is disturbed, all kinds of diseases can arise. Neutrophils, macrophages, and NK cells are immune cells that act against protozoan parasites by mediating innate responses (Lopes *et al.* 2012). These immune cells, together with dendritic cells, as vital keys in the initiation of adaptive immunity to produce different cytokines family (Melby *et al.* 2018). The intestinal Epithelial Cells (IECs) line is the surface of the intestinal epithelium, which plays vital functions within the absorption of nourishment, digestion of supplements, and as a defense against microbial infections and others.

IECs dysfunction causes illnesses (Kong *et al.* 2018; Novak and Mollen 2015). IECs will bind and identify Pathogen Associated Molecular Patterns (PAMPs) via Pattern Recognition Receptors (PRRs) during the early stages of the protozoan parasitic infection (Pott and Hornef 2012), which subsequently activates NF- $\kappa$ B to produce proinflammatory cytokines, for instance, IL-1 $\beta$ , IL-6, IL-8, IL-12, IFN- $\gamma$ , and TNF- $\alpha$  which stimulate Th1 type responses (Liu *et al.* 2017). IFN- $\gamma$  activates neutrophils and macrophages to perform infection clearance. Numerous studies have revealed the role of CD4 + T cells that produce IFN- $\gamma$  in the pathogenesis of protozoan parasites infection are involved in protection in vaccinated mice (Akira and Takeda 2004; Guo *et al.* 2009).

Antigen from the protozoan parasite also triggers the Th2-type immune response through the host and persuades anti-inflammatory cytokines productions, for example, IL-1, IL-4, IL-10, IL-5, IL-13, IL-18 (Gurung and Kanneganti 2016). These anti-inflammatory cytokines will repress the Th1 type responses, which are also represented by IFN- $\gamma$  production, and in contrast increasing the Th2 (IL-4, IL-5, and IL-13) and Th17 (IL-17) cytokine responses and activate the anti-inflammatory cytokine TGF- $\beta$ , which plays a crucial role and performances synergistically to counterbalance this Th1 type response, stimulates macrophages to produce NO (Nitric Oxide) to eradicate parasites (Kupani *et al.* 2021). Consequently, the Th1 type cytokine response is distinguished principally by IFN- production, while vulnerability to tissue damage by protozoan parasites is enormously reliant on the Th2-type cytokine response mediated by IL-4 (Muñoz-Carrillo *et al.* 2018).

## 5. Cytokines

Cytokines are small proteins at about 25 kDa size, formed by T cells, neutrophils, and macrophages. Cytokines have a fundamental role in stimulating and controlling the action of the immune response, including differentiation, proliferation, and production of cells (Ferreira *et al.* 2018). Cytokines function in two behaviors, influencing the manners of cells that release cytokines (autocrine) or disturb adjoining cells (paracrine) (Ferreira *et al.* 2018; Long *et al.* 2016). Cytokines are activated and triggered by binding to specific receptors. Some cytokines are even stable enough to influence distant cells (endocrine) but depend on their capability to enter

the circulation and on their half-life in the blood (Ferreira *et al.* 2018; Long *et al.* 2016; Murphy and Weaver 2017).

Toll-like receptors (TLRs) are proteins in the innate immune system which have a critical role by recognizing signals of the receptor from several types of pathogens that are processed by macrophages and dendritic cells, and at the same moment, deliver cytokines (Ozato *et al.* 2002). If the innate immune response is incompetent to eliminate the infections, therefore, the adaptive response will take charge by operating many of the same innate immune system instruments but directing them with far greater precision. A signal secreted by TLR will initiate the transcription factor NF- $\kappa$ B, which generates proinflammatory cytokines (Murphy and Weaver 2017; Mahla *et al.* 2013). More than 60 different cytokines are generated by specific types of cells that are able to influence many or only a few types of cells, depending on each cytokine receptor (Murphy and Weaver 2017).

## 6. Cytokines Groups

The cytokines varieties emitted from cells depend on the type of cells that are stimulated by the antigen and will affect the performance of other cells. Cytokines are categorized into seven groups: (1) IL-1 superfamily, (2) TNF superfamily, (3) IL-17 superfamily, (4) IL-6 superfamily, (5) Superfamily type I, and (6) Superfamily type II (7) Transforming Growth Factor Beta superfamily (Morán *et al.* 2013). All those types of cytokines are formed by a wide-ranging of cells, such as macrophages, B lymphocytes, T lymphocytes, endothelial cells, fibroblasts, mast cells, and various stromal cells. Cytokines can be formed by more than one type of cell (Liu *et al.* 2007; Muñoz-Carrillo *et al.* 2018; Morán *et al.* 2013).

### 6.1. IL-1 Superfamily

IL-1 cytokine family consists of 11 classes, for instance, IL-1 $\alpha$ , IL-1 $\beta$ , IL-1Ra, IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ , IL-36 $\delta$ , IL-36Ra IL-37, and IL-38. IL-1 was first defined as two main proteins, IL-1a and IL-1b, called human leukocytic pyrogen that produced fever. Exceed any other cytokine family, IL-1 cytokine family are densely associated with disastrous inflammation, and vice versa, perform specific resistance to infection and improve immune responses (Akdis *et al.* 2011; Muñoz-Carrillo *et al.* 2018; Xu *et al.* 2019).

## 6.2. TNF Superfamily

There are 19 ligands and 29 receptors in the Tumor Necrosis Factor Superfamily (TNFSF), which conduct a fundamental function in inflammation, monitoring the proliferation, differentiation and the apoptosis of the cells (Dostert *et al.* 2019). TNF- $\alpha$  works as several therapeutic roles in the body, for instance, immune-stimulation fight against infectious pathogens, tumors, sleep management, and embryonic enlargement. Parasitic, bacterial, and viral infections will disrupt the TNF distribution as a facilitator in protection to infection (Locksley *et al.* 2001). Tumor Necrosis Factor- $\alpha$  or TNF cytokine is an influential driver of endothelial cells (Murphy and Weaver 2017) and is a cell-signaling protein participating in systemic inflammation and become one of the cytokines which form in the acute stage (Muñoz-Carrillo *et al.* 2018). Plasma concentrations of the soluble TNF- $\alpha$  receptors sTNFRI and sTNFRII will bind to circulate TNF- $\alpha$  and control its activity, associate with parasitemia and the severity of diseases in *P. falciparum* malaria in Africa (Gonçalves *et al.* 2012).

## 6.3. IL-17 Superfamily

There are six family classes of IL-17 and known as a proinflammatory cytokine (Jin and Dong 2013). IL-17 is well-known in defense against extracellular pathogens and their influence in the development of autoimmune diseases. IL-17 is produced by Th17 cells,  $\gamma\delta$  T cells, and innate lymphoid cells. Autoimmune diseases that are complemented with chronic inflammation will powerfully influence the IL-17 cytokine by producing many signals to complicate the inflammatory factors. Nevertheless, IL-17 cytokine can also act as an anti-inflammatory in certain circumstances and controlling the immune homeostasis (Jin and Dong 2013; Kuwabara *et al.* 2017; Muñoz-Carrillo *et al.* 2018).

## 6.4. IL-6 Superfamily

The IL-6 family as Colony-Stimulating Factors (CSF) classes consist of IL-6, IL-27, IL-31, IL-35, Cilia Neurotropic (CNTF), Leukemia Inhibiting Factors (LIF), Oncostatin M (OSM), Cardiotrophin-1 (CT-1), and Cardiotrophin Like Cytokine (CLC) (Tanaka *et al.* 2014). Interleukin 6 (IL-6) has a crucial role in response to infections and tissue injuries via stimulation of acute-phase responses, hematopoiesis, B cell differentiation into antibody plasma cells, T cell

modulators, Th17 development (Muñoz-Carrillo *et al.* 2018; Tanaka *et al.* 2014).

## 6.5. Type 1 Superfamily

The type I cytokine family as hematopoietic classes consist of IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-13, IL-12, IL-15, IL-18, IL-21, and granulocyte-macrophage colony stimulation factors (GM-CSF) (Metcalf *et al.* 2020). Macrophages will secrete IL-12 and IL-18 for the development of type 1 cytokine response. While the secretion of the rest of the cytokines for the activation of the JAK/STAT pathway signaling to enhance the specificity for gene expression (Metcalf *et al.* 2020; Muñoz-Carrillo *et al.* 2018).

## 6.6. Type II Superfamily

Interferon (IFNs) and IL-10 belong to the type II superfamily. Interferon- $\gamma$  will promote macrophages to be more competently capable of extinguishing the intracellular and extracellular pathogens by stimulating target tissues. The infection upgrades macrophages to produce cytokines and raises the inflammatory response (Wu *et al.* 2014). Increased level of IFN- $\gamma$  production is interconnected with resistance to infection, while the decreased level of IFN- $\gamma$  is related to elevated vulnerability to malaria infection (Muñoz-Carrillo *et al.* 2018). At the same time, IL-10 plays an essential role between pro- and anti-inflammatory, immune responses and is crucial for affecting the clinical symptoms of *P. falciparum* infections (Moormann *et al.* 2009).

## 6.7. Transforming Growth Factor-beta Superfamily

Transforming Growth Factor Beta 1 or TGF- $\beta$ 1 is a secreted protein that acts in many cellular functions, such as cell growth regulatory including cell proliferation, cell differentiation, and apoptosis (Xu *et al.* 2019). If TGF- $\beta$  failed inactivation and signaling regulation, it will undergo apoptosis. TGF- $\beta$  will be identified by many cells because most of the cells have specific receptors to bind this protein (Kubiczkova *et al.* 2012). TGF- $\beta$ 1 is classified as human platelets with 25 kilodaltons of size and has an important key in wound healing (Tiemessen *et al.* 2003). TGF- $\beta$ 1 works in the regulation of the immune system, and conduct different performances on many different types of cell and at many different developmental stages. Leukocytes are the immune cells that secrete a high portion of TGF- $\beta$ 1 (Tiemessen *et al.* 2003; Wahl

*et al.* 2006). TGF beta influences many cell types as a strong anti-inflammatory initiator. The increasing level of TGF beta is associated with increased parasitemia in malaria infections (Moormann *et al.* 2009).

## 7. Cytokine Profile in Parasitic Infections

It is remarkably difficult to decide how immune mechanisms fight against or resist the infection of the parasite since there are different kinds of parasites with distinctive morphologies through their life cycle and settle in different locations within the host body's tissues. The protozoan parasite is much greater and more complex than viruses and bacteria. It always develops itself and constantly has an innovative and more sophisticated strategy to evade the host's immune system and have a life cycle in several phases of specific antigenicity, which will enable their survival from different cells, tissues, and hosts. More than 30% of people in the world are infected with protozoan parasites and frequently found in developing countries. When each of the hosts is not successful in eliminating protozoan infections, it often gives a fatal outcome, such as develop into chronic diseases, which sometimes ended up vague since the host is continuous as a reservoir of parasites for the rest of their lives (Ahmad *et al.* 2018; Matthys *et al.* 2011; Melby *et al.* 2018).

Fighting the parasitic infection will be challenging to the immune system. In addition, parasites contain many types with various forms. In order to survive, parasites will spread in different cells, tissues and have innovative and sophisticated mechanisms to escape the host immune system to infect other hosts. Parasites have several specific antigenicity stages to survive in many circumstances (Mabbott 2018).

Neutrophils, macrophages, and NK cells will facilitate the innate response to eliminate the extracellular protozoan parasites (Gurung and Kanneganti 2016). NK cells together with cytokine-activated macrophages are key to innate responses to intracellular parasites, and together with dendritic cells, will conduct initiate adaptive immunity if innate immunity fails the task (Gurung and Kanneganti 2016; Melby *et al.* 2018). Innate immunity protects from the protozoan parasitic infection through the Intestinal Epithelial Cells (IEC) which will bind to PAMP via PRRs (Pott and Hornef 2012)

and directly activates Th1 type responses to induce the NF- $\kappa$ B to produce proinflammatory cytokines, such as IL-1 $\beta$ , IL-6, IL-8, IL-12, IFN- $\gamma$ , and TNF- $\alpha$  (Liu *et al.* 2017). One of the well known cytokines such as IFN- $\gamma$  activates neutrophils and macrophages to work in cleansing protozoan parasites infections (Guo *et al.* 2009).

Previous studies using human and animal models state that the IFN- $\gamma$  from NKT cells initiates protection, while TNF- $\alpha$ , IL-1, and IL-8 increased tissue damage. Increased-level of IFN- $\gamma$  level production is linked with resistance to infection, while decreased-level of IFN- $\gamma$  is related to increased susceptibility to infection. Consequently, it is reflected that IFN- $\gamma$  delivers protection against infection by the activation of neutrophils and/or macrophages (Balato *et al.* 2009; Locksley *et al.* 2001; Muñoz-Carrillo *et al.* 2018).

The protozoan parasite likewise initiates the Th2-type immune response and produce the anti-inflammatory cytokines such as IL-4, IL-10, IL-5, and IL-13, which will suppress Th1 type responses by IFN- $\gamma$  production, and at the same time, increase Th2 (IL-4, IL-5, and IL-13) and Th17 (IL-17) cytokine responses (Gurung and Kanneganti 2016). Subsequently, it promotes the TGF- $\beta$  as an anti-inflammatory cytokine to collaborate to respond to this Th1 type response, which initiates the macrophages to secrete Nitric Oxide (NO) to extinguish the parasite's infection (Kupani *et al.* 2021). IFN- $\gamma$  cytokine production is classified from the Th1, which will endure tissue damage (Liu *et al.* 2017; Muñoz-Carrillo *et al.* 2018; Rosloniec *et al.* 2002). Th1 is highly dependent on IL-4 produced by Th2 (Rosloniec *et al.* 2002).

## 8. EBV Viremia Reactivation is Induced by Malaria

EBV+ B cells are regularly linked with EBV-DNA levels in the plasma (Calattini *et al.* 2010). A study presented that EBV-DNA levels in the plasma of children and pregnant women with malaria increased compared with those without malaria, suggesting that EBV could be reactivated during malaria infection (Piriou *et al.* 2012). Circulating viral load is also correlated with increased exposure to malaria and also to the severity and number of disease stages, implying that *P. falciparum* infection influences reactivating viral replication (Daud *et al.* 2015; Rasti *et al.* 2005). Other studies confirm that

an increase in plasma EBV viral load is demonstrated during the endemic Burkitt Lymphoma development (Asito *et al.* 2011).

Former studies have analyzed EBV reactivation by Malaria *P. falciparum* in EBV-infected B cells. The CIDR1 $\alpha$  domain of PfEMP1 protein induced the virus to lytic replication, and CIDR1 $\alpha$  promotes the EBV in the peripherals blood mononuclear cells to proliferate (Chêne *et al.* 2007). This mechanisms have been displayed in Figure 1.

EBV infects 95% of the world population including people from developing countries due to high chronic exposure and high risks of carcinogen. EBV infection continues for life after primary contact. EBV infects epithelial cells and B cells through saliva as well as blood, the B cells are stimulated and transformed to long-lived (immortal) cells by virus latent genes and the epithelial cells permit complete lytic replication and virus production and secretion and as the primary protection, the innate

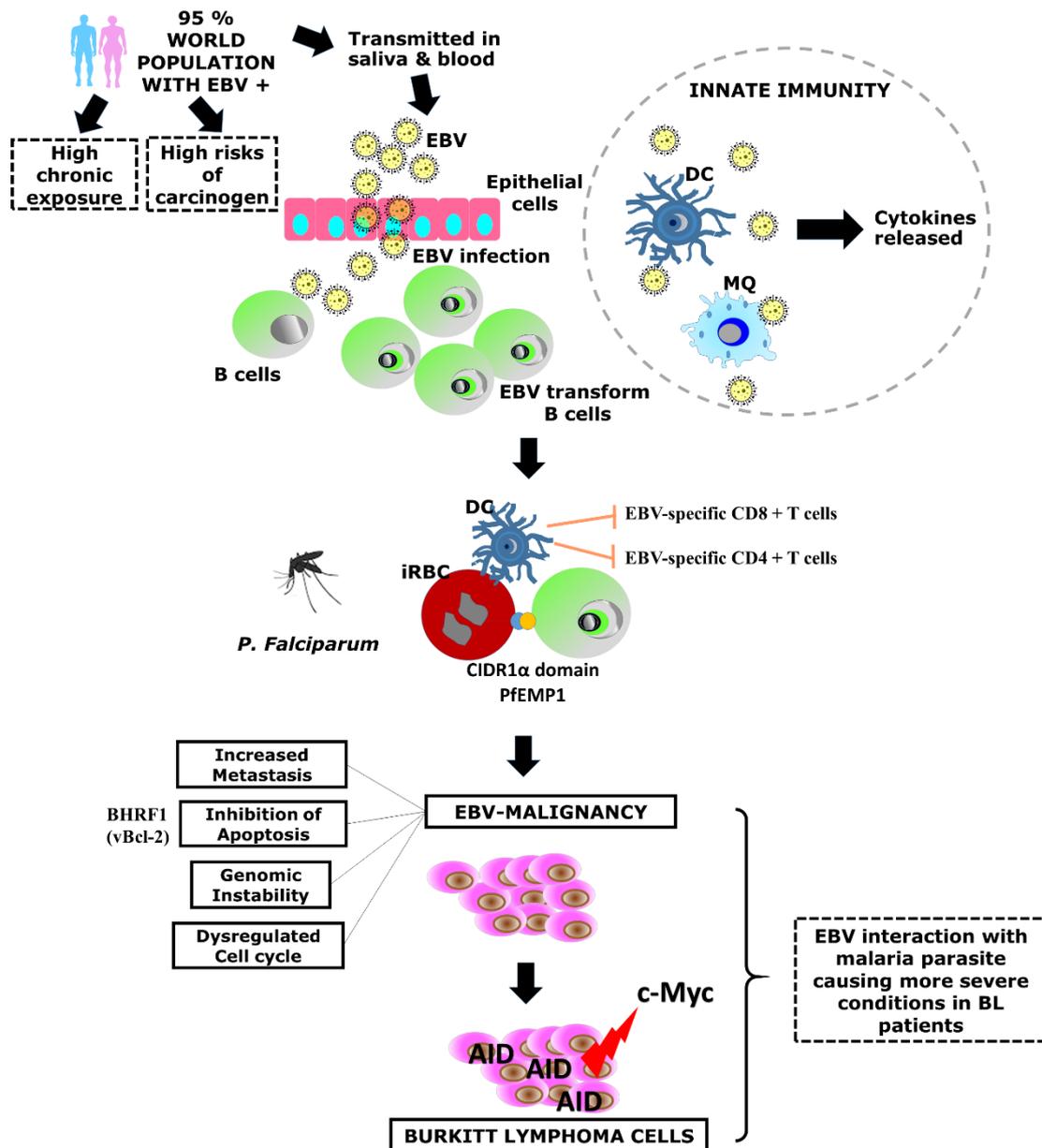


Figure 1. Epstein-Barr Virus and *P. falciparum* Malaria leads to Burkitt Lymphoma

immune cells such as macrophages, neutrophils, monocytes, eosinophils, mast cells, together with dendritic cells also play a vital role in the induction of adaptive immunity to produce different regulatory cytokines (Thorley-Lawson 2015; Muñoz-Carrillo *et al.* 2018). Every time B cell divides, a number of EBV gene products provide benefits for B cell survival and transform oncogenic host cells or allow the survival of clones that are normally prohibited and later can increase metastasis, inhibit the apoptosis, making genomic instable, and dysregulated the cell cycle. These mechanisms can trigger EBV to cause severe diseases and malignancy. One of the malignancies which is known as EBV associated with *P. falciparum* is Burkitt Lymphoma, as a form of non-Hodgkin's lymphoma which starts in immune B-cells, a very fast-growing human tumor and can cause easily fatal because of the impaired immunity. Red blood cells infected with *P. falciparum* (iRBC) will bind to B cells infected with EBV by fastening the CIDR1 $\alpha$  domain of *P. falciparum* Erythrocyte Membrane Protein 1 (PfEMP1) (Thorley-Lawson *et al.* 2016). This condition will direct EBV to activation and lytic replication. EBV-infected B cells will expand and will increase the production of Activation-Induced cytidine Deaminase (AID). AID mediates the breakdown of DNA and activates c-Myc oncogenes, and induces somatic mutations. The AID will also promote chromosomal rearrangement, especially the translocation between Ig promoter regions and c-Myc oncogene, which drives the proliferation and differentiation of B cells in GC (Taylor *et al.* 2015). The presence of EBV in the activated and immortalized B-cell will promote apoptosis resistance through its BHRF1 (vBcl-2) gene product, which subsequently may lead to the survival of malignant B-cell clones. Moreover, the attachment of iRBC with the dendritic cells (DCs) prime to a modification of DC functions, which causes suppression of the EBV-specific T-cell immunity (CD8 + and CD4 + T cells), with the result that the loss of regulatory effect the expansion of EBV-infected B cells and be part of the cause of emergent Burkitt Lymphoma clones (Chêne *et al.* 2007; Taylor *et al.* 2015).

## 9. Burkitt Lymphoma

Burkitt Lymphoma is a tumor of the jaw and face found in children and recognized as a fast-growing human tumor in a form of non-Hodgkin's lymphoma.

Burkitt's lymphoma starts in B-cells and is associated with compromised immunity and can quickly become lethal if left untreated. Burkitt's lymphoma is common in young children in Africa who have malaria and Epstein-Barr virus infections. Malaria infections weaken the immune system's response to the Epstein-Barr virus that will change the infected B-cells into malignancy cells (Chêne *et al.* 2007; Thorley-Lawson 2015; Molyneux *et al.* 2012).

Burkitt Lymphoma (BL) is an aggressive non-Hodgkin B-cell lymphoma and causally associated with EBV and overexpression of oncogene c-Myc. The WHO categorizes BL into three clinical groups: endemic, sporadic and immunodeficiency-related. The endemic form of BL is 100% related to malaria and EBV, with EBV genome and gene products present in all tumor cells. The detailed mechanism underlying EBV and B-cell malignancy stays unclear but has been explored in a recent review (Molyneux *et al.* 2012). Initial B-cell infection by EBV leads to growth transformation and formation of pre-malignant long-lived memory B-cells. EBNA-1 protein is an EBV latent protein expressed required for maintenance of the viral genome in dividing B-cells and is expressed 100% in endemic BL. The expression of EBNA3 genes (i.e., EBNA3A-C) during initial B-cell transformation leads to methylation and silencing of cellular Bim-promotor, making cells non-apoptotic when overexpressing c-Myc, thus favoring malignant B-cell outgrowth (Paschos *et al.* 2009).

The interaction of B cells with *P. falciparum* is a key factor in malaria. B cell activation and hypergammaglobulinemia in malaria have been well clarified experimentally and clinically. A study has revealed that erythrocytes infected by *P. falciparum* will directly activate B cells via the domain of CIDR1 $\alpha$  of *P. falciparum* Erythrocyte Membrane Protein 1 (PfEMP1) (Molyneux *et al.* 2012). PfEMP1 preferentially binds and activates memory B-cells, which can proliferate and rearrange the c-Myc gene to the active promotor region of Ig heavy or light chains, under the influence of EBV-induced recombinase genes, ultimately leading to Burkitt Lymphoma (Thorley-Lawson *et al.* 2016).

Increased numbers of B cells with EBV infection are frequently linked with the EBV-DNA levels in the plasma of malaria patients. Prior studies have afforded an understanding of *P. falciparum*-induced EBV reactivation, initiated by a study on the interaction between EBV-infected B cells and the CIDR1 $\alpha$

domain of PfEMP1 protein, which directly switches viruses to lytic replication and CIDR1 $\alpha$  increases the production of EBV in peripheral blood mononuclear cells (Calattini *et al.* 2010).

Interaction of EBV+ memory B-cells with malaria surface proteins leads to B-cell activation, differentiation and growth by inducing high levels of c-Myc and causing genetic translocation and oncogenesis. BL is endemic to areas where malaria cases are still high, such as in Brazil, Papua New Guinea, and equatorial Africa. Findings showed that malaria patients had increased EBV-DNA loads in blood (Piriou *et al.* 2012; Wilmore *et al.* 2015), and there is a direct correlation between endemic BL and increased *P. falciparum* antibody titers (Graham and Lynch 2020).

## 10. Conclusion

The immune system has its own way of eliminating viral and parasitic infections, but to determine the complex mechanisms of the immune system dealing with these two pathogens would be informative knowledge. However, in-depth and extensive research is needed to classify the immune system which functions to treat two infections at a time, especially when these two pathogens interaction could lead to severe malignancy such as Burkitt Lymphoma.

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