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Current Opinion in Virology

Animal models of Epstein Barr virus infection

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Epstein Barr virus (EBV) was the first human tumor virus to be described. Despite its discovery now more than fifty years ago, immune control of this virus is still not very well understood and no vaccine is available. This knowledge gap is due in part to the lack of a preclinical small animal model which can faithfully recapitulate EBV infection and immune control, and would allow testing of EBV specific vaccine candidates. With the advent of mice with reconstituted human immune system compartments (HIS mice) during the past decade this is changing. We will discuss which aspects of EBV infection and its immune control can already be modeled in HIS mice, and which shortcomings still need to be overcome in order to recapitulate the immunobiology of oncogenic EBV infection.

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Current Opinion in Virology 2015, **13**:6–10

This review comes from a themed issue on **Animal models for viral diseases**

Edited by **Alexander Ploss** and **Christopher Walker**

For a complete overview see the Issue and the Editorial

Available online 2nd April 2015

http://dx.doi.org/10.1016/j.coviro.2015.03.014

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Introduction

Epstein Barr virus (EBV) is a highly successful γ-herpesvirus in the human population. It persistently infects more than 90% of human adults, and is controlled by cell-mediated immune responses in most infected individuals for life [1]. Primary infection is thought to occur via saliva exchange and transepithelial access of viral particles to B cells in submucosal secondary lymphoid tissues. In these target cells, EBV initially replicates vertically through proliferation of the latently infected B cells. Expression of six EBV nuclear antigens (EBNAs), two latent membrane proteins (LMPs), two EBV encoded RNAs (EBERs) and around 40 microRNAs drives B cells into proliferation [2]. These activated B cells then undergo differentiation leading to EBV persistence in long-lived memory B cells and reactivation into lytic replication and virus production in plasma cells [3]. The epigenetic silencing of the EBV genome and the down-regulation of latent EBV antigen expression, which is associated with B cell differentiation, are both required for the function of Zta (BZLF1), which initiates transcription of around 80 lytic EBV genes [4]. Reactivation most likely occurs through B cell receptor triggering by the cognate antigen at submucosal sites. There, EBV can infect epithelial cells via the basolateral side for an additional round of lytic replication and subsequent shedding into the saliva for transmission [5,6].

Because of possibly only vertical replication via B cell proliferation initially, EBV viral loads only peak and can cause symptoms after four to six weeks of primary infection [7,8]. This symptomatic primary EBV infection, which preferentially occurs when primary EBV infection is delayed into adolescence, is called infectious mononucleosis (IM) or Pfeiffer's glandular fever [9]. The associated symptoms are linked to the immunopathologic expansion of cytotoxic $CD8^+$ T cells, which are also thought to primarily exert immune control of the virus [1]. Consistent with this important role of $CD8^+$ T cells, immunosuppression that compromises T cell function, leading to uncontrolled EBV infected B cell proliferation, can be treated by adoptively transferring EBV specific T cell lines; individuals that lack EBV specific antibodies can still control persistent EBV infection [10,11]. Loss of this EBV specific immune control contributes to the development of EBV associated malignancies. Indeed, this virus was discovered more than fifty years ago as the first human tumorvirus [12,13]. It is now known to be associated with B cell derived tumors like Burkitt's and Hodgkin's lymphomas, as well as epithelial cell derived tumors like nasopharyngeal and a subset of gastric carcinomas [2]. Apart from T cell mediated immune control, however, little is known about immune compartments that are additionally required to establish and maintain EBV specific immune control. At the time of clinical presentation of IM, the innate immune responses that precede the associated massive $CD8^+$ T cell expansion have left only few traces. Moreover, the exclusive tropism of EBV for humans made it impossible to study this important human pathogen in a preclinical *in vivo* model system until recently. In this review, we will summarize and outline to which extent mice with human immune system components, that are reconstituted from neonatally transferred human $CD34^+$ hematopoietic progenitor cells, (HIS mice) [14] have and can be used to address these questions.

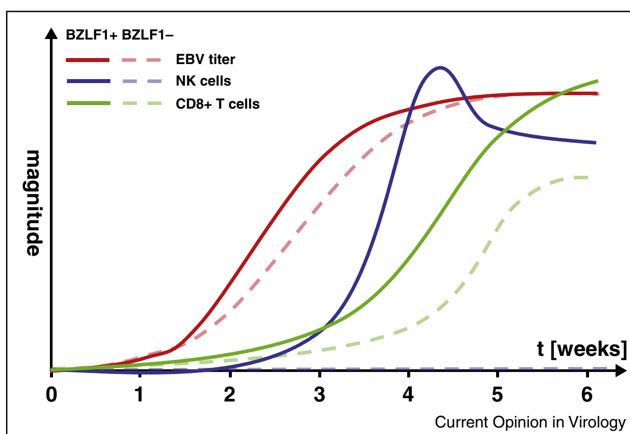
EBV infection and tumorigenesis in HIS mice

EBV was the first human pathogen to be studied in HIS mice [15]. Depending on the dose, infection of HIS mice

with EBV can range from asymptomatic viral persistence in B cells to lymphoproliferative disease (LPD), similar to what is seen in immunocompromised individuals [16,17]. Mice inoculated with an intermediate dose of the most commonly used laboratory EBV strain, B95-8, isolated from an American IM patient [18], results in viremia after four to six weeks (Figure 1), progressive weight loss and splenomegaly. This is due to EBV-infected B cell proliferation and reactive $CD8^+$ T cell expansion (Figure 1) [19•]. As such, acute, symptomatic EBV infection seen in IM patients can be modeled in HIS mice.

Latent and lytic EBV infection may occur to different extents in HIS mice, depending on the viral stain used for inoculation. Upon infection with the B95-8 strain, only a minority of infected B cells enter the lytic replication cycle, as evidenced by the low levels of lytic immediate early transactivator BZLF1 expression [20–22] and the similar to wild-type viremia profile during infection with a BZLF1 KO virus (Figure 1) [20]. The majority of infected B cells express all eight latent EBV proteins. This has been confirmed by immunohistochemical co-staining for EBNA2 and LMP1 and an abundance of Cp promotor driven EBNA1 mRNA expression [16,23]. This pattern of EBV gene expression is termed latency III and is commonly found in polymorphic post-transplant lymphoproliferative disease or AIDS-associated Diffuse Large B Cell Lymphoma of the immunoblastic type [2]. It has been suggested that B cells expressing latencies I and II with reduced latent EBV antigen expression (typically found in Burkitt lymphoma and Hodgkin lymphoma, respectively) are also present upon HIS mouse infection

Figure 1



Dynamics of wild-type and lytic replication deficient EBV infection and immune control in HIS mice. Viremia of wild-type (BZLF1+) and lytic replication deficient (BZLF1–) B95-8 EBV infection differ only transiently at early time points after EBV infection (mainly week three). NK cell expansion peaks at week four controlling lytic EBV replication, while EBV infection is prevented from further increasing by lytic and latent EBV antigen specific T cell responses at weeks five and six after inoculation of HIS mice.

with EBV [22–24]. However, these seem to contribute to a small percentage of all EBV-infected B cells in conventional HIS mice. The use of mice in which both human fetal $CD34^+$ hematopoietic progenitor cells and thymus/liver tissue are transplanted (BLT mice) may be more likely to support the development of B cells harboring latencies I and II, possibly due to better immune restriction of latency III B cells by T cells and better secondary lymphoid tissue development in BLT mice of the NOD-*scid* mouse background [22,25]. Without germinal center development in secondary lymphoid tissues HIS mice primarily harbor transitional and naïve B cells [26].

Furthermore, the HIS mouse model has proved useful to study the *in vivo* biology of specific latent and lytic EBV gene products by employing recombinant knock-out viruses [20,22,27•,28••] or to compare different EBV strains [21]. Along these lines, infection of HIS mice with an EBV deficient in EBNA3B, shown to be dispensable for transformation *in vitro*, resulted in increased LPD and tumor formation due to aggressive B cell proliferation and reduced secretion of CXCL10, a T cell attracting chemokine, thus identifying EBNA3B as a viral tumor suppressor [27•]. In another study HIS mice were infected with an EBV strain called M81, isolated from a Chinese nasopharyngeal carcinoma patient, and this resulted in an increased frequency of lytically replicating cells compared to B95-8 and higher viremia [21]. Lytic activity is, however, not required for stable infection of HIS mice [22], but surprisingly may enhance the efficiency of tumorigenesis [20,22]. Finally, complete latency III transformation and the expression of LMP1 does also not seem to be required for EBV persistence, because T cell help might substitute for LMP1 function [28••]. Thus, lytic and latency III infection by EBV and their respective associated malignancies can be modeled in HIS mice.

Innate immune control of EBV infection in HIS mice

Since innate responses to EBV might be responsible for preventing symptoms of IM, it is important to increase the understanding of these early responses to EBV. Innate immune compartments such as dendritic cells (DCs) and natural killer (NK) cells were suggested to play a role in the control of EBV infection. Conventional DCs (cDCs) and the plasmacytoid DCs (pDCs) as well as NK cells reconstitute in HIS mouse models [29–33]. These DC subsets have been shown to sense EBV using different PRRs. While pDCs recognize unmethylated CpG DNA motifs present in the dsDNA of EBV particles via Toll-like receptor (TLR) 9 [34,35], cDCs can recognize EBERs that are released from infected cells using TLR3 or the intracellular receptor RIG-I [36].

PDCs were required for immune control of EBV infection in a transfer model of human peripheral blood mononuclear cells (PBMCs) into immunocompromised mice.

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