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PhD Dissertation Defense

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Exploring the dynamics of primary Epstein-Barr virus infection using a novel rabbit model

by

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Date & Venue

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Lecture Theatre: Yanah Theatre

* Location: 2C010 located on 2nd floor 'C' block male side.

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Abstract

Epstein-Barr virus (EBV) is a common herpesvirus asymptomatically carried by over 90% of the world population. However, in certain circumstances, the virus can lead to life-threatening diseases. Although the virus was isolated over 55 years ago, several fundamental aspects of the biology of EBV and the mechanism by which this virus induces pathology remain unknown. One major obstacle has been the lack of a suitable small animal model for EBV infection. We have recently shown that healthy rabbits are susceptible to EBV infection, and the virus establishes long-term latent infection typically seen in humans. The main objective of this dissertation was to delineate the early events of primary EBV infection using in a novel rabbit model of EBV infection. Additionally, the rabbit model was utilized to assess the efficacy of an EBV based virus like particle (VLP) vaccine.

In this study, EBV was inoculated intravenously into the experimental rabbits, and PBS was injected into the control animals, with and without immunosuppression. Using various histopathological, biochemical and molecular techniques, plasma, PBMCs and spleens from rabbits were analyzed. Several important aspects related to primary EBV infection was investigated. The results indicated that both, immunocompetent and immunosuppressed animals were readily susceptible to EBV infection on intravenous inoculation. However, in immunosuppressed animals, we observed marked splenomegaly and widespread infection. Following primary EBV infection, the virus infected naïve B cells (IgM+, CD20+, CD21+, CD79a+). Infected splenic B-cells expressed varying sets of viral latent (EBER+, EBNA1+, EBNA2+, LMP1+), and to a lesser extent, lytic (BZLF1+) products. Notably, co-expression of latent and lytic proteins was not observed. Infected cells in type 0/1 latency (EBER+) were small and proliferating (Ki67+). By contrast, cells in type 2/3 latency (LMP1+) were large, non-proliferating (Ki-67-) and p53+. Finally, infected B-cells were commonly observed in splenic follicles but did not express germinal center marker, BCL-6.

Since EBV is etiologically associated with a number of malignant and non-malignant conditions, a prophylactic vaccine against this virus could help to reduce the burden of many of these diseases. Previously, it was reported that an EBV VLP vaccine was highly immunogenic and produced strong humoral response in mice. However, since EBV does not infect mice, the efficacy of the VLP in preventing EBV infection could not be addressed. Thus, for the second main aim of the project, the rabbit model of EBV infection was used to evaluate an EBV-VLP. Animals were vaccinated intramuscularly, and PBS was injected in the control group. Animals were then challenged with EBV. Animals vaccinated with 2 doses of VLP, elicited higher antibody responses to total EBV antigens compared to animals receiving 1 dose. Vaccinated animals also elicited both IgM and IgG to EBV specific antigens, VCA and EBNA1. Analysis of peripheral blood and spleen for EBV copy number, indicated that the viral load in both of these compartments was significantly lower in animals receiving 2-dose of the VLP vaccine.

In conclusion, this study showed that primary EBV infection in vivo, leads to the virus targeting naïve B cells, which express varying viral latency programs. Moreover, a population of the infected cells proliferate in the lymphoid follicles, but do not appear to express the germinal center marker. The VLP vaccine elicited antibody response to EBV antigens, but the vaccine was not successful in preventing primary EBV infection. Taken together, the findings of this study indicate that rabbit model of EBV infection can be used for elucidating the biology of EBV and evaluating potential vaccine candidates.

Keywords: Epstein-Barr Virus, primary infection, germinal center, latent proteins, virus-like particles, antibody response, rabbit model.