2017

A Review of Epstein Barr Virus Immunity, Pathogenesis and Immunotherapies

Heather Stuart
heather8547@my.uri.edu

A Review of Epstein Barr Virus Immunity, Pathogenesis and Immunotherapies

Epstein – Barr Virus (EBV), a member of the Herpesviridae family, is commonly known as the cause of infectious mononucleosis. While EBV infection has acute effects, its primary significance in human health stems from its association with multiple cancers resulting from chronic infection. EBV first establishes infection in epithelial cells of the oropharynx, where it is lytic, and later establishes latent infection in B cells, where it exists in latency for remainder of the host's lifetime. Dendritic cells and natural killer cells are first to control expansion of the infection followed by cytotoxic T cells and helper T cells. Through mechanisms involving EBV lytic proteins, BGLF5, BNLF2, gp42, BILF1, BZLF1, EBV evades the initial immune response and adapts a latency program where EBNA1 and microRNAs enable the virus to further evade host immune mechanisms throughout all latency stages. During the latent stage, EBV acts on cell proliferative and cancer protecting mechanisms to cause cancers of epithelial and lymphatic origins.

First discovered in Burkitt's lymphoma, EBV is now known to cause nasopharyngeal carcinoma, gastric carcinoma, Hodgkin's and non-Hodgkin's lymphomas. EBV's major oncogene, LMP1, induces signaling pathways involving NF-kB and PI3K to cause cellular proliferation and survival. EBV's nuclear antigen, EBNA1, which is present in all latency stages, is able to induce anti-apoptotic effects through inhibition of p53. EBNA2, the EBNA3 family, LMP2, EBERs, and microRNAs also aid in cellular proliferation, survival, and migration through mechanisms involving PI3K, PKR, and induction of cellular gene expression.

A wide range of approaches are being studied to treat EBV-associated cancers, including vaccines, adoptive cell therapies, and monoclonal antibodies reviewed here. Vaccination and cell therapy aim to enhance T cell response to specific EBV latent antigens including EBNA1, LMP1, and LMP2. Many vaccines aim to increase the number of cytotoxic T cells that recognize infected cells that present the selected EBV antigen at their surface. Clinical trials demonstrate that increased cytotoxic T cell levels track with median survival. Adoptive cell therapy uses autologous T cells specific for viral antigens that are expanded ex vivo and reinfused into patients. This approach has been shown to be effective in treating tumors and in preventing relapse. Monoclonal antibody therapy directed at EBV antigens, although less developed an approach, has shown efficacy in preclinical studies targeting EBV antigen BARF1. This strategy holds promise for a new way to treat EBV-associated cancer that may stand on its own or be combined with the others. Although there is currently no vaccine to prevent EBV from establishing chronic infection, these therapies show potential to treat its pathogenic sequelae.