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EBV-associated lymphomas in adults

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Epstein-Barr virus (EBV) is a ubiquitous γ-herpes virus that infects most people but results in life-threatening diseases in only a small subset. Persons who are unable to maintain the virus in its latent state can develop uncontrolled EBV-driven lymphoproliferative disorders and lymphomas. EBV-associated lymphomas are well characterized in patients with known defects in cellular immunity as occurs post-transplantation or HIV/AIDS but are increasingly recognized in patients without overt immunodeficiencies. Improved understanding of the biology of these lymphomas and the role EBV plays in lymphomagenesis offer the opportunity for improved therapies targeted at important signaling pathways and immunotherapy specific against EBV viral antigens.

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Introduction

Epstein-Barr virus (EBV) is a ubiquitous γ-herpes virus that infects >90% of normal adults through contact with oral secretions. After primary infection, the virus remains in an asymptomatic latent state within resting B-cells for the lifetime of the host and cytotoxic T-cells (CTLs), both $CD8^+$ and $CD4^+$, and natural killer (NK) cells are primarily responsible for containing the infection [1]. Under circumstances in which the host's cellular immune system fails to control EBV-induced B-cell proliferation, infected carrier B-cells can transform from their latent state into malignant cells. The type and duration of the host's defect in EBV immune surveillance determines the clinical presentation, which is usually aggressive. Thus, the term "EBV-associated lymphomas" encompasses a heterogeneous group of aggressive B-cell and NK/T-cell lymphomas which arise in patients with and without overt

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impairments in cellular immunity [2]. Management of EBV-associated lymphomas involves restoration of the host's immune response to EBV whenever possible in addition to therapy directed at the malignant cells. Despite improved understanding of the molecular mechanisms that underpin EBV-driven lymphomagenesis, management of these conditions is largely unsatisfactory and novel therapeutic approaches are necessary.

Latency patterns of EBV infection

In vitro, EBV can transform B-lymphocytes into cells that proliferate in an unregulated fashion [3]. *In vivo*, EBV preferentially infects B-lymphocytes by binding to the cell surface CD21 receptor and HLA class II molecules as a co-receptor. After primary infection, the EBV episome largely remains in a latent cycle in resting memory B-cells in most patients. While perpetually present within the host, EBV has deftly developed strategies to evade the host's CTLs by altering its pattern of gene expression. The EBV genome normally codes for nearly 100 viral proteins, but EBV-infected resting memory cells evade immune recognition by limiting the gene expression to nine viral latent proteins in varying patterns. The six nuclear antigens EBNAs-1, -2, -3a, -3b, -3c, and -LP are responsible for maintaining the viral genome as well as controlling the expression of three latent membrane proteins: LMP-1, -2a, and -2b. Also expressed are 2 small non-coding RNAs, EBER-1 and EBER-2, as well as BamHI-A rightward transcripts (BART) [4,5].

Three distinct patterns of latency programs are associated with different types of lymphomas. The first pattern of latency (type I) is selective expression of EBNA-1 only which is seen in Burkitt's lymphoma (BL). A second pattern of latency (type II) is the expression of EBNA-1 along with LMP-1 and LMP-2 and is found in Hodgkin's lymphoma (HL) and peripheral T-cell lymphoma (PTCL). The third pattern of latency (type III), also known as the "growth program," is commonly found in post-transplantation lymphoproliferative disorders (PTLD) and is characterized by the expression of all nine latent cycle EBV antigens (Table 1). The latency pattern determines the susceptibility of the infected cells to immunotherapeutic maneuvers as will be discussed later in greater detail.

EBV and lymphomagenesis

EBV was originally discovered in cultured lymphoblasts from Burkitt's lymphoma patients in 1964 [6]. It has been defined as a "carcinogenic agent" by the World Health Organization (WHO) since 1997 and its primary role in lymphomagenesis in immunosuppressed patients (type III latency) is well characterized. However, its oncogenic role in immunocompetent patients is less clear and it may simply be a passenger virus and/or be acting as a co-factor. The latent gene expression program is directly responsible for inducing B-cell transformation through its interactions with the host and utilizes numerous mechanisms to control the activation and differentiation of B-cells, alter cellular gene transcription, and constitutively activate key cell-signaling pathways.

LMP-1 is the main transforming protein of EBV and can act as an oncogene as evidenced by its ability to induce B-cell lymphomas in transgenic mice [7]. It structurally mimics the CD40 ligand and can bind to the CD40 receptor which is normally found on the surface of B-cells [8]. In this way, LMP-1 expression results in ligand-independent constitutive activation of the nuclear factor-κB (NF-κB) pathway and provides a growth signal to B-cells. Other signaling pathways that are modulated by LMP-1 include JAK/STAT, extracellular signal regulated kinase (ERK), mitogen activated protein kinase (MAPK), interferon-regulatory factor 4 (IRF4), and Wnt pathways which are essential for B-cell immortalization

Table 1
EBV latency programs and associated lymphomas.

Program	EBER	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	Lymphoma
Type 1	+	+	−	−	−	−	BL, plasmablastic
Type 2	+	+	−	−	+	+	HL, AITL, Extranodal T/NK-cell
Type 3	+	+	+	+	+	+	PTLD, AIDS-related