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ONCOGENESIS OF EPSTEIN-BARR VIRUS

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Epstein-Barr Virus (EBV), also known as Human Herpes Virus 4 (HHV-4) is a gamma herpes virus, that was first isolated in tumour tissue samples of Burkitt lymphoma (BL). The virus was discovered to be the causative agent of the aggressive sub-Saharan cancer BL over 50 years ago, and subsequently was linked to several other cancers. Most notably, Nasopharyngeal carcinoma, gastric adenocarcinoma, Hodgkin lymphoma and post-transplant lymphoproliferative disorder.

Despite its lack of popularity outside medical and microbiology circles, the Center for disease control and prevention (CDC) states that 9 out of 10 adults have been infected with EBV in their life. The virus is spread through saliva and typically causes infectious mononucleosis (IM), although many infections are asymptomatic. EBV tends to stay on in its latent cycle. During the latent infection, viral oncoproteins such as latent membrane protein 1 (LMP1) and LMP2 mimic CD40 and B-cell receptor signaling, respectively, activating pro-survival pathways (NF-κB, PI3K/Akt) and fostering uncontrolled proliferation

The pathophysiology of oncogenesis depends partly on which cells have been infected by the virus. While EBV shows remarkable trophism to B lymphocytes, it also infects epithelial cells and NK/T cells.

As per various studies, 4 different types of gene expression are known – they are known as Latency Types. Each Latency type promotes different types of gene expression as it affects varying transcriptional start sites and promotors. The genome consists of numerous Epstein-Barr Nuclear Antigens (EBNA), [EBNA 1, 2, 3A, 3B, 3C & Leader Protein], as well as Latent Membrane Protein [LMP 1 & 2]. The composition of EBNA and LMP varies with each Latency Type. For example, Latency Type 1 only has the expression of one viral protein – EBNA 1 and a few non-coding RNAs, whereas Latency Type 3 expresses all types of EBNA and LMPs. This potent arsenal of genes and viral proteins allow the virus to evade the human immune system and epigenetically modify the host DNA, causing cancer.

The mechanisms of oncogenesis have been investigated extensively throughout the years, and the essential notion is as follows:

EBNA1 initiates viral replication in before mitosis, maintaining the viral genome. EBNA2 activates transcription of the host cell's MYC oncogene by interacting with transcription factors. EBNA3 and LMP1 inhibit apoptosis, protecting the infected cell from NK and T cells. EGFR is a cell receptor that promotes continued growth, particularly that of malignant cells. LMP binds to the receptor and activates it. Furthermore, EGFR and LMP can travel through the plasma as exosomes, recruiting more cells.

While the aforementioned cancers have shown direct links the Epstein-Barr virus, researchers are currently finding new links with other cancers, for example breast cancer. This work focuses on the pathophysiology of oncogenesis of this common yet rather elusive virus.