Cooperating oncogenes in viral associated cancer

Epstein-Barr virus (EBV)

Epstein-Barr virus (EBV) is a gamma herpesvirus that infects the vast majority of the world's population (Jung and Speck, 2013). Although EBV infection is usually asymptomatic or causes mild flu-like symptoms, it has been linked to the development of malignant disorders such as Hodgkin's lymphoma. This report examines the relationship between EBV and Hodgkin's lymphoma in depth, with a focus on the role of the EBV-encoded protein LMP1, the use of transgenic mouse models (LMP1 line 39), the potential role of murine leukaemia virus (MoMLV) and insertional mutagenesis in the development of Hodgkin's lymphoma.

EBV is an enveloped virus that contains DNA and belongs to the herpesvirus family. It is related to cytomegalovirus, varicella-zoster virus, herpes simplex virus and human herpesviruses 6, 7, and 8. EBV and human herpesvirus 8 are linked to the development of some human tumours (Thompson, 2004). EBV infects nearly 90% of the adult population worldwide and causes individuals to be infected for the rest of their lives. It is spread through salivary contact. During acute infection, the virus penetrates the squamous epithelium of the oropharynx and later creates a latent infection in B cells. The precise sequence of infection between epithelial cells and lymphocytes remains unknown. The virus survives in circulating memory B cells in carriers. In vitro, EBV has the ability to turn resting B lymphocytes into continuously developing lymphoblastoid cell lines (Thompson, 2004).

The identification of EBV genomes in Reed-Sternberg cells, the hallmark cells of Hodgkin's lymphoma, led to the original discovery of the link between EBV and the disorder (Weiss et al., 1989).

Structure and Function LMP1

In Hodgkin's lymphoma cells, the latent membrane protein 1 (LMP1), one of the important viral proteins encoded by EBV, is expressed. LMP1 is a transmembrane protein with six transmembrane domains, an N-terminal cytoplasmic domain, and a C-terminal cytoplasmic domain, among other functional domains (Küppers, 2002). It works as a receptor involved in B-cell activation called CD40 that is constitutively activated (Küppers, 2002). LMP1 has been linked to the emergence of Hodgkin's lymphoma and is essential for the survival and growth of EBV-infected B cells.

Through the activation of a number of signalling pathways, including NF-B, MAPK/ERK, JAK/STAT, and PI3K/AKT, LMP1 exerts its carcinogenic effects. LMP1 affects gene expression, encourages cell survival, triggers cellular proliferation, and modifies the host immunological response via activating various pathways. Additionally, LMP1 aids in the development of latent EBV infection and aids in immune surveillance evasion (Dawson et al., 2012; Ma et al., 2012).

Role of LMP1 in EBV-Associated Malignant Diseases

Particularly in the subtype of Hodgkin's lymphoma linked to EBV infection, LMP1 is frequently expressed. Hodgkin and Reed-Sternberg cells, which are the typical tumour cells in Hodgkin's lymphoma, exhibit its expression. LMP1 participates in immune evasion strategies and aids in the survival and growth of these tumour cells (Weiss et al., 1989; Murray et al., 2003).

Latent membrane protein 1 (LMP1) encourages a number of processes that aid in the growth, survival, epithelial-mesenchymal transition (EMT), angiogenesis, and metastasis of cancer cells. By causing a cadherin-integrin "switching" process that results in the elevation of mesenchymal markers such vimentin, N-cadherin, fibronectin, Twist, Snail, and matrix metalloproteinase and the downregulation of certain proteins like E-cadherin and -catenin, it causes EMT in epithelial cells (Lo et al., 2021). This change promotes the invasion and migration of epithelial cells, aiding in the spread of cancer. By encouraging the synthesis of pro-angiogenic substances like VEGF, FGF, and IL-8, LMP1 also encourages angiogenesis. It promotes cell development by increasing cytokines like IL-6 and growth factors like EGFR. LMP1 also promotes anti-apoptotic proteins (including Bcl-2 and A20) that shield cancer cells from harmful signals, helping cells survive (Lo et al., 2021).

LMP1 not only affects epithelial tumour cells, but it can also influence the behaviour of other cell types in the tumour microenvironment (TME). Cancer-associated fibroblasts (CAFs) are a group of fibroblasts found in the TME that play an important role in tumour growth (Lo et al., 2021). CAFs are activated by LMP1 and other tumor-derived factors, which then produce growth factors, cytokines, and proteases. These substances promote cell proliferation while degrading the extracellular matrix, allowing tumour cells to move and infiltrate neighbouring tissues. CAFs have been found in nasopharyngeal carcinoma (NPC) tissue biopsies, and their density has been linked to a poor prognosis in NPC patients. LMP1-positive tumours are thought to be more effective at inducing CAF development (Lo et al., 2021).

Moloney Murine Leukemia Virus (MoMLV)

Retroviruses are RNA viruses that multiply through the mechanism of reverse transcription (Goff, 2007). Given its capacity to cause leukaemia in mice and its potential uses in gene therapy, it has undergone substantial research (Coffin et al., 1997).

The envelope, lipid bilayer obtained from the host cell membrane, capsid holding the viral RNA genome, and reverse transcriptase enzyme make up the retroviral structure of MoMLV (Goff, 2007). When infected, the viral genome is made up of two identical copies of positive-sense RNA, which is reverse-transcribed into DNA.

MoMLV has a clear replication cycle. When a virus enters a cell, its envelope protein interacts with the receptor to assist the virus fuse and enter the cytoplasm. Within the cytoplasm, the viral

genome undergoes a process of reverse transcription into DNA, followed by the viral DNA integration into the host genome (Coffin, Hughes and Varmus, 1997).

Insertional mutagenesis

Insertional mutagenesis is the modification of host gene expression or interruption of gene function caused by the integration of foreign DNA into the host genome, such as MoMLV. This process can result in a variety of outcomes, including proto-oncogene activation, tumour suppressor gene inactivation, and genomic instability (Cavazzana-Calvo et al., 2004).

MoMLV-induced insertional mutagenesis has been linked to the development of several cancers. Viral integration can cause cellular transformation and cancer by activating proto-oncogenes and disrupting tumour suppressor genes (Hacein-Bey-Abina et al., 2008).

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