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(REVIEW ARTICLE)

Literature Review: The Significance of Epstein-Barr Virus and Latent Membrane Protein 1 (LMP-1) Detection and Their Clinical Implications in Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC), a type of epithelial cancer, is frequently found in Southeast Asia and Southern China. The Epstein-Barr Virus (EBV) significantly contributes to the development of NPC by producing latent proteins, particularly Latent Membrane Protein 1 (LMP-1). This protein acts as an oncoprotein, activating several signaling pathways, including NF-κB, JAK/STAT, and PI3K/Akt. Consequently, this factor facilitates cellular proliferation, angiogenesis, and the inhibition of apoptosis. A multitude of investigations have established a correlation between the expression of LMP-1 and both the malignancy of tumors and the clinical outcomes of individuals afflicted with KNF. LMP-1 detection can be achieved through immunohistochemistry (IHC), polymerase chain reaction (PCR), or in situ hybridization (ISH) techniques, each exhibiting varying degrees of sensitivity and specificity. Furthermore, LMP-1 serves as a critical diagnostic and prognostic indicator, and it also presents a potential target for molecular interventions in nasopharyngeal cancer.

Keyword: Epstein-Barr Virus; Latent Membrane Protein-1 (LMP-1); Nasopharyngeal Carcinoma (NPC); Oncogenic Signaling Pathway; Biomarkers; LMP-1 Detection Methods

1. Introduction

Nasopharyngeal carcinoma (NPC), a type of cancer that starts in the epithelial cells, shows a specific geographical pattern, with greater rates of occurrence in Southeast Asia, Southern China, and some areas of North Africa (1). Unlike other malignancies of the head and neck, nasopharyngeal carcinoma (NPC) is strongly associated with infection with the Epstein–Barr Virus (EBV). This virus, which can cause cancer, is a kind of herpesvirus that can stay dormant in epithelial cells and lymphocytes. The presence of Epstein-Barr virus (EBV) is virtually always seen in cases of non-keratinizing undifferentiated carcinoma (KNF), which highlights its important role in the disease's development (2).

Latent Membrane Protein 1 (LMP-1) is the main protein produced by the Epstein-Barr virus (EBV) during its latent phase. This protein acts as an oncoprotein, mimicking the CD40 receptor's function. As a result, it starts many cellular signaling pathways, including NF-κB, JAK/STAT, and PI3K/Akt. These pathways' activation thus promotes cell growth, the creation of new blood vessels, and resistance to programmed cell death, all of which are key features of cancer cells (3). Furthermore, studies indicate a connection between higher LMP-1 expression and both the clinical grade of the tumor and its aggressive behavior. However, the exact cause-and-effect link is still being studied (4).

Besides its involvement in changing cells, LMP-1 also affects the tumor microenvironment. It does this by encouraging lymphocyte infiltration and affecting the local immune system. This phenomenon highlights the immune system's ability

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to recognize and evade the immune response in EBV-infected KNF cells, which is characterized by a complicated interplay between tumor cells and the host's immune system (2). Therefore, LMP-1 is relevant not only as a cause of disease but also as a possible biomarker for diagnosis and prognosis, and as a target for molecular therapies in KNF (5).

This review will analyze the biological significance of the Epstein-Barr Virus, especially the LMP-1 protein, in the development of nasopharyngeal cancer. The study will also assess different approaches for identifying LMP-1. Improving the diagnosis and treatment of nasopharyngeal carcinoma (NPC) is the main goal, and this will be achieved by employing molecular biomarkers.

2. Epstein-Barr virus

2.1. Structure and Characteristics of the Epstein-Barr Virus

The Epstein–Barr Virus (EBV), a virus with double-stranded DNA (dsDNA), is classified under the Herpesviridae family. It belongs to the Gammaherpesvirinae subfamily and the Lymphocryptovirus genus. The virus's structure is defined by four basic parts: a core that carries the viral DNA, an icosahedral capsid that is around 120–180 nm broad, a tegument layer, and a lipid envelope. The viral envelope has glycoproteins on its surface, which are essential for the virus to bind to and enter host cells (7). The Epstein-Barr virus (EBV) has a genome that is around 172 kilobase pairs (kbp) long. The genome comprises roughly eighty genes. These genes are involved in the virus's replication, the regulation of gene expression, and the mechanism by which the virus alters host cells, potentially leading to cancer (8).

Genetically, Epstein-Barr virus (EBV) is classified into two main types: EBV type 1 (A) and EBV type 2 (B). Differences in the sequences of the EBNA2 and EBNA3 genes (6) are used to identify these kinds. The two varieties are found in separate geographical areas. Type 1 is most common in Asia and Europe, while type 2 is predominantly found in Africa. The viral life cycle includes two primary stages: the lytic phase and the latent phase. During the lytic cycle, the virus actively replicates, which leads to the creation of new virions. In contrast, the latent phase only shows a limited range of gene expressions. These latent genes, such as EBNA1–6, LMP1–2, and EBERs, are crucial for the development of cancer and the virus's long-term survival in the host cell (7).

The Epstein-Barr virus (EBV) has a strong predilection for nasopharyngeal epithelial cells and B lymphocytes. The virus infects these cells when the viral glycoprotein gp350/220 binds with the CD21 (CR2) receptor on the cell surface (9). Once inside a cell, Epstein-Barr virus (EBV) has a few tricks up its sleeve. It can dodge the immune system's defenses by blocking the presentation of antigens via MHC class I molecules. Additionally, EBV alters the body's cytokine responses. This unusual trait permits the Epstein-Barr virus (EBV) to stay in a lasting, inactive state, while simultaneously contributing to the development of malignancies including nasopharyngeal carcinoma and other lymphomas (8).

2.2. EBV Cycle

The Epstein-Barr Virus (EBV) infection cycle involves two main stages: the lytic phase and the latent phase. Both of these stages are important in the development of illnesses, such as nasopharyngeal cancer. During the lytic phase, Epstein-Barr virus (EBV) uses its viral glycoproteins, gp350 and gp42, to attach to CD21 and HLA class II receptors on the surface of host cells. This attachment allows the virus to penetrate epithelial cells or B lymphocytes. After the virus enters a cell, it brings its DNA into the cell's nucleus. This starts a process of active replication, making new viral particles. These particles then allow the infection to spread to neighboring cells (10).

In contrast, during the dormant phase, Epstein-Barr virus (EBV) keeps its genetic material in an episomal form within the nucleus, without creating new viral particles. At this stage, the virus produces multiple latent genes, including LMP-1, EBNA (Epstein-Barr Nuclear Antigen), and LMP (Latent Membrane Protein). These genes are crucial for the host cells' transformation and ongoing survival. This latent cycle allows the virus to persist in the human body for a long time. It can then reactivate, entering the lytic phase, when the immune system is weakened or inflammation continues. Reactivation of Epstein-Barr virus (EBV) may increase the risk of developing epithelial cancers, such as nasopharyngeal carcinoma and lymphoproliferative disorders (11).

2.3. EBV in Nasopharyngeal Carcinoma

The Epstein-Barr Virus (EBV) is a key factor in the development of Nasopharyngeal Carcinoma (NPC), particularly the non-keratinizing subtype, which is common in Southeast Asia. When EBV infects cells, it causes nasopharyngeal epithelial cells to change. This happens through the expression of latent proteins, such as Latent Membrane Protein 1 (LMP-1), EBNA-1, and LMP-2A. These proteins then activate cancer-related signaling pathways, including NF-κB, JAK/STAT, and PI3K/Akt. Consequently, these processes promote increased cell proliferation, migration, and resistance

to apoptosis in the affected cells (12). Furthermore, the interaction between Epstein-Barr virus (EBV) expression and host genetic factors, such as variations in the MMP-11 gene, can worsen the cancer process. This happens by changing the tumor microenvironment and promoting the breakdown of the extracellular matrix (13).

Additionally, EBV promotes epigenetic changes and increases RNA stability, which speeds up the development of nasopharyngeal carcinoma (NPC). Recent studies suggest that EBV can create a positive feedback loop between the FOXD1 gene and the NAT10 enzyme, thus supporting the growth and spread of nasopharyngeal cancer cells (12). This finding shows that EBV acts not only as an infectious agent but also as a regulator of host oncogenic gene expression through epitranscriptomic control. Currently, biomarkers such as LMP-1, plasma EBV DNA, and viral non-coding RNA are being developed to help with early diagnosis and to evaluate how well treatments are working in patients with nasopharyngeal carcinoma (NPC) (10).

3. Latent Membrane Protein – 1 (LMP-1)

3.1. Structure of Latent Membrane Protein-1 (LMP-1)

Latent Membrane Protein-1 (LMP-1) is a key oncoprotein produced by the Epstein–Barr Virus (EBV) during the latent phase of type II infection, particularly in nasopharyngeal carcinoma (NPC) and Hodgkin lymphoma. This membrane protein has six transmembrane domains, a short cytoplasmic N-terminal region, and a long C-terminal region that is involved in signal transduction (15). Functionally, LMP-1 acts like the "EBV equivalent of CD40," mimicking CD40 receptor activation in B or epithelial cells, which leads to pro-survival signals (16).

As a result, LMP-1 activation triggers several signaling pathways, including NF-κB, JNK, p38 MAPK, and PI3K/Akt, which then increase the expression of anti-apoptotic genes such as Bcl-2, A20, and survivin (17). Therefore, LMP-1 significantly affects the cellular microenvironment, promoting tumor cell growth and survival.

3.2. The Role of LMP-1 in NPC Tumorigenesis

Latent Membrane Protein-1 (LMP-1), the primary oncoprotein of the Epstein–Barr Virus (EBV), triggers the transformation of nasopharyngeal epithelial cells through the activation of several cellular signaling pathways, specifically NF-κB, JAK/STAT, and PI3K/Akt, which collectively promote the proliferation and survival of cancer cells. The activation of NF-κB by LMP-1 leads to an increased expression of pro-proliferative genes, including cyclin D1, and anti-apoptotic genes such as Bcl-2, thereby providing a growth advantage to the infected cells (19). Moreover, LMP-1 activates STAT3, which in turn elevates the production of survivin and Mcl-1, two essential proteins that prevent cellular death (20).

3.3. LMP-1 as a biomarker in nasopharyngeal carcinoma

The expression of Latent Membrane Protein-1 (LMP-1) shows a correlation with the clinical stage and severity of nasopharyngeal carcinoma (NPC) (18). Higher levels of LMP-1 are often seen in patients with advanced-stage disease, suggesting its importance in the disease's development and its potential as a biological marker for tumor invasiveness (21). The activation of LMP-1 triggers oncogenic signaling pathways, including NF-κB and PI3K/Akt, which promote cancer cell growth and help the cells resist programmed cell death (22). Furthermore, LMP-1 is significantly linked to both nodal and distant metastasis, with increased expression associated with a greater number of positive lymph nodes and a higher chance of tumor spread (23). This approach is characterized by an increased synthesis of adhesion molecules and angiogenic factors, such as VEGF, which facilitate tissue invasion (24). Furthermore, LMP-1 contributes to therapeutic resistance, encompassing both radioresistance and resistance to cisplatin-based chemotherapy, through its regulation of the anti-apoptotic gene Bcl-2 and its influence on autophagy (25).

LMP-1 functions as a predictive biomarker and can be employed alongside other molecular markers, including KYNU and lncRNA FAM3D-AS1, to improve clinical risk stratification and predict therapeutic outcomes (21). Elevated LMP-1 expression is often associated with reduced survival rates and an increased likelihood of recurrence; consequently, routine LMP-1 testing may provide significant prognostic value (26). The utilization of LMP-1 as a comprehensive biomarker could enhance diagnostic accuracy, assessment of disease progression, and therapeutic effectiveness in patients with NPC (23).

4. LMP-1 Detection Methods

4.1. Histopathological Detection

Histopathological methods are crucial for detecting the presence of Latent Membrane Protein 1 (LMP-1) within nasopharyngeal cancer tissues, employing FFPE (formalin-fixed paraffin-embedded) specimens. This technique allows for the extended preservation of both tissue architecture and viral antigens, which is indispensable for subsequent analyses, including immunohistochemistry and in situ hybridization (27). A network of nasopharyngeal carcinoma (NPC) exists, where LMP-1 expression is often concentrated in areas of epithelial cells undergoing neoplastic transformation, a finding that correlates with tumor proliferation. Consequently, this methodology provides a fundamental foundation for subsequent specialized assays targeting other EBV proteins, such as EBER or EBNA (18).

4.2. Detection by Immunohistochemistry (IHC)

Immunohistochemistry (IHC) is the primary method for detecting LMP-1 in nasopharyngeal carcinoma (NPC) tissue. This is due to its simplicity, accessibility, and ability to locate proteins directly in the tissue. The basis of immunohistochemistry (IHC) is the specific interaction between antibodies and target antigens. Monoclonal antibodies, such as CS1-4, are used to identify the LMP-1 epitope (27). LMP-1 expression was assessed by examining the amount of cytoplasmic or membrane staining in tumor cells. This was done using a semi-quantitative scoring system that considered both the proportion of stained cells and the intensity of the staining (18). The main advantages of this method are its simplicity and its ability to assess both tissue structure and antigen expression. However, its disadvantages include variability in antibodies and staining procedures, which can affect the sensitivity of the results (28).

4.3. Other Methods

In addition to immunohistochemistry (IHC), the identification of Epstein-Barr virus (EBV) employs molecular techniques such as polymerase chain reaction (PCR) and in situ hybridization (ISH) for the detection of EBER. PCR exhibits considerable sensitivity, enabling the detection of EBV DNA even in minute samples, while ISH allows for the direct visualization of viral RNA transcripts within the tissue. Although less frequently used in nasopharyngeal carcinoma (NPC) due to their inherent complexity and the necessity for fresh specimens (29), Western blotting and flow cytometry have been applied. Generally, ISH offers greater specificity compared to PCR; however, PCR is more adept at detecting EBV with high sensitivity, particularly in the early identification of EBV in latent NPC cases.

4.4. Relationship between LMP-1 Expression and Clinical Implications

The expression of Latent Membrane Protein-1 (LMP-1) plays a crucial role in determining the clinical severity of nasopharyngeal carcinoma (NPC). Increased LMP-1 expression is associated with more advanced TNM stages and poorer histological differentiation. LMP-1's activation of the TGF-β/Smad3/NRP1 pathway promotes epithelial-mesenchymal transition (EMT), thereby increasing the invasive and proliferative capabilities of the primary tumor (30). Meta-analyses have also shown similar correlations, revealing a strong link between LMP-1 positivity and lymph node metastases (31).

Beyond its role in tumor proliferation, LMP-1 influences both therapeutic efficacy and patient prognosis. Extracellular vesicles that harbor LMP-1 can initiate the p38 MAPK pathway, thereby contributing to resistance to radiation therapy and a decrease in sensitivity to chemotherapy (32). Furthermore, patients with positive LMP-1 expression exhibited a higher rate of recurrence and a shorter overall survival duration when contrasted with those displaying negative LMP-1 expression (33). Recent findings support the potential of LMP-1 as a predictive biomarker, reflecting disease severity, metastatic potential, and clinical outcomes in nasopharyngeal carcinoma (NPC) (34).

5. Conclusion

The Epstein–Barr Virus (EBV) plays a crucial role in the development and progression of nasopharyngeal carcinoma (NPC), primarily through the expression of latent genes such as Latent Membrane Protein-1 (LMP-1). LMP-1 functions as a viral oncoprotein, activating diverse signaling pathways, including NF-κB, JAK/STAT, and PI3K/Akt, thereby promoting cellular proliferation, angiogenesis, invasion, and resistance to apoptosis. These molecular alterations highlight EBV, specifically LMP-1, as a key driver of carcinogenesis in NPC, and they underscore the importance of understanding viral–host interactions in disease progression.

LMP-1 demonstrates considerable clinical utility as a diagnostic and prognostic biomarker. Elevated LMP-1 expression is consistently associated with advanced TNM stage, poor differentiation, increased lymph node involvement, and distant metastases. LMP-1 contributes to treatment resistance, particularly in response to radiotherapy and platinum-based chemotherapy, through the activation of p38 MAPK and the upregulation of anti-apoptotic pathways. These observations imply that assessing LMP-1 expression could refine risk stratification and potentially enable more personalized treatment approaches for patients with nasopharyngeal carcinoma (NPC).

Accurate identification of LMP-1 expression in clinical specimens has been achieved through various detection methods, including immunohistochemistry (IHC), PCR, and in situ hybridization (ISH). The utilization of these techniques supports early diagnosis, the monitoring of disease progression, and the evaluation of therapeutic effectiveness. Presently, the available evidence suggests that integrating Epstein-Barr virus (EBV) and LMP-1 profiling into routine clinical practice may enhance diagnostic accuracy, deepen biological understanding, and promote the development of targeted therapies for nasopharyngeal cancer.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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