World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Oncogenic role of LMP1 expression in Epstein-Barr virus associated with nasopharyngeal carcinoma: A literature review

Arya Satya Rajanagara [1,*], Chabib Fachry Albab [1], Ardan Mulyarajasa Hanifullah [2] and Marsha Zahrani [1]

[1] *Faculty of Medicine, Airlangga University, Surabaya, East Java, Indonesia.*
[2] *Faculty of Medicine, University of Wijaya Kusuma Surabaya, Surabaya, East Java, Indonesia.*

World Journal of Advanced Research and Reviews, 2023, 17(01), 063–066

Publication history: Received on 24 July 2022; revised on 29 July 2022; accepted on 31 July 2022

Article DOI: https://doi.org/10.30574/wjarr.2023.17.1.0874

Abstract

Nasopharyngeal carcinoma (NPC) is a malignant carcinoma that appears in the epithelial lining of the nasopharyngeal mucosa. Genetic predisposition, environmental risk factors, nutritional risk factors, and Epstein-Barr virus (EBV) infection are the main risk factors for NPC. Epstein-Barr virus, a human cancer-associated virus, is present in more than 90% of people worldwide. Latent Membrane Protein 1 (LMP1) has been identified as the main Epstein-Barr virus converting oncoprotein. LMP1 was shown to be present in NPC tumor tissues, suggesting a potential role for LMP1 in EBV-mediated carcinogenesis. LMP1 exerts several oncogenic properties and has the ability to transform epithelial cells through the activation of numerous signaling pathways and the control of the expression of different oncogenes and tumor-suppressor genes. the process by which tumor traits such cell proliferation, apoptosis resistance, invasion and motility, and angiogenesis are produced and maintained.

Keywords: Latent Membrane Protein 1 (LMP1); Epstein-Barr virus (EBV); Nasopharyngeal carcinoma; Oncogenic

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant carcinoma that develops in the nasopharyngeal mucosa's epithelial lining. Southern China, notably the provinces of Guandong and Guangxi, North-East India, the Arctic area, Southern Asia, and Northern Africa all have high rates of NPC. The World Health Organization (WHO) suggested three groups for histological classification of NPC in 1978: Type I (keratinizing squamous cell carcinoma), Type II (non-keratinizing carcinoma), and Type III (undifferentiated carcinoma). The main risk factors for NPC are genetic predisposition, environmental risk factors, dietary factors, and Epstein-Bar virus (EBV) infection [1].

More than 90% of people worldwide are infected by the human cancer-associated virus Epstein-Barr virus (EBV) [2]. There are three types of EBV infections: type I, type II, and type III latencies. Only EBV nuclear antigen-1 (EBNA-1), latent membrane protein- 1 (LMP1), LMP2, and EBV early RNA (EBER) expressions are linked to type II latent infection of NPC by EBV. Due to their capacity to attract a variety of cellular genes and interaction with a number of vital cellular signaling pathways, EBNA1 and LMP1 are the main oncogenes of EBV, increasing the severity and pathogenesis of the disease by inhibiting apoptosis, promoting cell proliferation, and causing metastasis. The majority of NPC patients were found to have significant levels of antibodies against EBV antigens during testing, the link of Epstein Barr virus was first established. By using a radioactive EBV probe to detect EBV DNA in the epithelial cells of NPC patients, the link between EBV and NPC was directly proven [1]. As the primary Epstein-Barr virus converting oncoprotein, latent membrane protein 1 (LMP1) has been found. Nasopharyngeal carcinoma, like other EBV-related malignancies, frequently expresses LMP1 [3].

* Corresponding author: Arya Satya Rajanagara
Faculty of Medicine, Airlangga University, Surbaya, East Java, Indonesia.

Copyright © 2023 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution Liscense 4.0.

In this literature review, we present summaries from a number of journals and discuss in greater detail about LMP1 expression in EBV and the role of LMP1 as an oncogenic factor.

2. LMP1 Expression in EBV

LMP1 may assist in EBV-mediated carcinogenesis, according to the finding that LMP1 is present in NPC tumor tissues. More than 70% of the sera from NPC patients had LMP1 antibodies [4]. However, the reported frequencies of LMP1 expression vary between research. This mismatch can be a result of the sensitivity and specificity of the LMP1 expression detection methods used. Despite the fact that first western blotting analyses revealed modest and inconsistent levels of LMP1 protein expression in NPC tissues [5], Later research using RT-PCR technology indicated significantly higher expression frequencies (>80%) [6]. Similar to this, a more recent study found that over 90% of NPC patients have LMP1 expression by RT-PCR in nasopharyngeal swabs [7]. In comparison to other EBV-associated cancers like EBV-positive Hodgkin's disease, immunoreactivity to LMP1 is often mild in NPC, with the frequency of LMP1 expression by immunostaining in the range of 20–60% [8]. However, the relevance of this diverse expression of LMP1 in NPC has not been thoroughly addressed. The staining pattern is highly varied among those that are positive for LMP1 expression and is occasionally only identified in a small fraction of NPC cells. Early stage NPC and carcinoma in situ express LMP1 more consistently than late stage illness,4 suggesting that LMP1 may speed up the course of the disease. It has been demonstrated that some epithelial cells are hazardous when LMP1 is expressed at high levels [9]. High levels of LMP1 expression may also trigger an immunological response. To prevent the host immune response system from being activated, EBV may modify the expression level of LMP1. It's interesting to note that LMP1-positive NPCs have a better prognosis than LMP1-negative instances [10]. Therefore, increased LMP1 expression may not promote NPC in vivo development. On the other hand, NPC cells may be given the growth advantage in vitro even with modest levels of LMP1 expression. In our lab, we found that relatively low levels of LMP1 expression in NP cells are sufficient to cause the invasive phenotypes and anchorage-independent growth morphological alterations that are linked to LMP1 expression [11].

3. The Role of LMP1 as An Oncogenic Factor

Through the activation of many signaling pathways and the modulation of the expression of various oncogenes and tumor-suppressor genes, LMP1 exert multiple oncogenic characteristics and possess the capacity to convert epithelial cells. The production and maintenance of tumor characteristics, such as cell proliferation, resistance to apoptosis, invasion and motility, and angiogenesis, may be how viral oncogenes promote the transformation of epithelial cells [12,13]. Additionally, LMP1 influences the generation of cytokines and chemokines, antigen presentation, and interactions between cells. By triggering a group of immune-associated proteins, LMP1 also mediates a variety of immunomodulatory actions that protect tumor cells infected with viruses from immune attack.

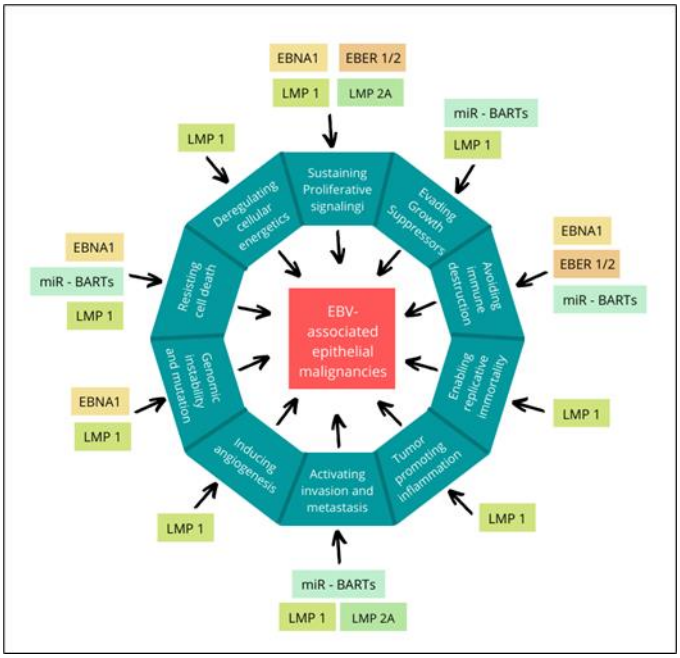

Figure 1 The Role of LMP1 as oncogenic factor [2].

A transmembrane protein called LMP1 functions as a constitutively active TNF receptor 1. Numerous signaling pathways, including NF-B, JNK-p-38, PI3K-AKT, ERK-MAPK, and JAK-STAT, are activated. Collectively, these pathways control the expression of numerous downstream cellular targets, which support LMP1's oncogenic properties. By activating growth factor receptors and downregulating cell cycle regulators, LMP1 can promote the development of NPC cells [14,15]. LMP1 can increase the production of anti-apoptotic proteins or deactivate pro-apoptotic proteins to improve cell survival. Additionally, it promotes angiogenesis by inhibiting the degradation of the protein hypoxia inducible factor-1 (HIF-1) and increasing the expression of the vascular endothelial growth factor (VEGF) [16]. In addition to inducing epithelial–mesenchymal transition (EMT), LMP1 was reported to induce cancer stem/progenitor-like cells in NPC cells, possibly by activating the Hedgehog signaling pathway [17,18]. EBV-associated cancer patients with positive LMP1 expression had significantly worse survival than those with negative expression, according to a meta-analysis of 3752 individuals included in 32 studies.

4. Conclusion

The human EBV infection process results in the appearance of the protein LMP1. LMP1 promotes a number of immunomodulatory processes that defend tumor cells infected with viruses from immune attack. One of the oncogene factors that can cause nasopharyngeal cancer through a number of different molecular pathways is LMP1.

Compliance with ethical standards

Conflict of interest statement

There is no conflict of interest in this study.

References

[1] Borthakur P, Kataki K, Keppen C, Khamo V, Medhi S, Deka M. Expression of Epstein Barr Virus encoded EBNA1 and LMP1 oncoproteins in nasopharyngeal carcinomas from Northeast India. Asian Pacific Journal of Cancer Prevention. 2016 Jul;17(7):3411-6.

[2] Tsao SW, Tsang CM, To KF, Lo KW. The role of Epstein–Barr virus in epithelial malignancies. The Journal of pathology. 2015 Jan; 235(2):323-33.

[3] Chen YP, Zhang WN, Chen L, Tang LL, Mao YP, Li WF, Liu X, Zhou GQ, Sun Y, Kang TB, Zeng MS. Effect of latent membrane protein 1 expression on overall survival in Epstein-Barr virus-associated cancers: a literature-based meta-analysis. Oncotarget. 2015 Oct; 6(30):29311.

[4] Xu J, Ahmad A, D'Addario M, Knafo L, Jones JF, Prasad U, Dolcetti R, Vaccher E, Menezes J. Analysis and significance of anti-latent membrane protein-1 antibodies in the sera of patients with EBV-associated diseases. The Journal of Immunology. 2000 Mar;164(5):2815-22.

[5] Young LS, Dawson CW, Clark D, Rupani H, Busson P, Tursz T, Johnson A, Rickinson AB. Epstein—Barr virus gene expression in nasopharyngeal carcinoma. Journal of General Virology. 1988 May; 1;69(5):1051-65.

[6] Brooks L, Yao QY, Rickinson AB, Young LS. Epstein-Barr virus latent gene transcription in nasopharyngeal carcinoma cells: coexpression of EBNA1, LMP1, and LMP2 transcripts. Journal of virology. 1992 May; 66(5):2689-97.

[7] Lin SY, Tsang NM, Kao SC, Hsieh YL, Chen YP, Tsai CS, Kuo TT, Hao SP, Chen IH, Hong JH. Presence of Epstein-Barr virus latent membrane protein 1 gene in the nasopharyngeal swabs from patients with nasopharyngeal carcinoma. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2001 Mar; 23(3):194-200.

[8] Sarac S, Akyol MU, Kanbur B, Poyraz A, Akyol G, Yilmaz T, Sungur A. Bcl-2 and LMP1 expression in nasopharyngeal carcinomas. American journal of otolaryngology. 2001 Nov; 22(6):377-82.

[9] Hammerschmidt WO, Sugden BI, Baichwal VR. The transforming domain alone of the latent membrane protein of Epstein-Barr virus is toxic to cells when expressed at high levels. Journal of virology. 1989 Jun; 63(6):2469-75.

[10] Hu LF, Chen F, Zhen QF, Zhang YW, Luo Y, Zheng X, Winberg G, Ernberg I, Klein G. Differences in the growth pattern and clinical course of EBV-LMP1 expressing and non-expressing nasopharyngeal carcinomas. European Journal of Cancer. 1995 Jan; 31(5):658-60.

[11] Tsao SW, Wang X, Liu Y, Cheung YC, Feng H, Zheng Z, Wong N, Yuen PW, Lo AK, Wong YC, Huang DP. Establishment of two immortalized nasopharyngeal epithelial cell lines using SV40 large T and HPV16E6/E7 viral oncogenes. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2002 Jun;1590(1-3):150-8.

[12] Tsao SW, Wang X, Liu Y, Cheung YC, Feng H, Zheng Z, Wong N, Yuen PW, Lo AK, Wong YC, Huang DP. Establishment of two immortalized nasopharyngeal epithelial cell lines using SV40 large T and HPV16E6/E7 viral oncogenes. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2002 Jun;1590(1-3):150-8.

[13] Dawson CW, Port RJ, Young LS. The role of the EBV-encoded latent membrane proteins LMP1 and LMP2 in the pathogenesis of nasopharyngeal carcinoma (NPC). Semin Cancer Biol. 2012 Apr; 22: 144–153.

[14] Miller WE, Earp HS, Raab-Traub N. The Epstein-Barr virus latent membrane protein 1 induces expression of the epidermal growth factor receptor. Journal of virology. 1995 Jul; 69(7):4390-8.

[15] Lo AK, Huang DP, Lo KW, Chui YL, Li HM, Pang JC, Tsao SW. Phenotypic alterations induced by the Hong Kong-prevalent Epstein-Barr virus-encoded LMP1 variant (2117-LMP1) in nasopharyngeal epithelial cells. International journal of cancer. 2004 May;109(6):919-25.

[16] Wakisaka N, Kondo S, Yoshizaki T, Murono S, Furukawa M, Pagano JS. Epstein-Barr virus latent membrane protein 1 induces synthesis of hypoxia-inducible factor 1α. Molecular and cellular biology. 2004 Jun; 15;24(12):5223-34.

[17] Horikawa T, Yang J, Kondo S, Yoshizaki T, Joab I, Furukawa M, Pagano JS. Twist and epithelial-mesenchymal transition are induced by the EBV oncoprotein latent membrane protein 1 and are associated with metastatic nasopharyngeal carcinoma. Cancer research. 2007 Mar; 67(5):1970-8.

[18] Port RJ, Pinheiro-Maia S, Hu C, Arrand JR, Wei W, Young LS, Dawson CW. Epstein–Barr virus induction of the Hedgehog signalling pathway imposes a stem cell phenotype on human epithelial cells. The Journal of Pathology. 2013 Nov; 231(3):367-77.