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Epstein–Barr Virus Associated Nasopharyngeal Carcinoma and the Role of Viral Circular RNAs: A Review Study

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Abstract
Nasopharyngeal carcinoma is a malignant tumor of the upper respiratory tract's epithelial cells that is more common in Southeast Asia, the Middle East, and North Africa than elsewhere in the world. According to research, Epstein-Barr virus plays an important part in the development of this cancer.Persistent EBV infection in nasopharyngeal epithelial cells promotes tumorigenesis by activating key signaling pathways, including NF-κB and PI3K/AKT, via viral genes such as LMP1 and EBERs. This leads to cell cycle dysregulation, immune evasion, and enhanced survival of malignant cells. EBV has been shown to generate specific circular RNAs (circRNAs) from the BART and RPMS1 regions, including circRPMS1 and circBART2.2, which modulate host miRNAs, trigger immune-related pathways such as IRF3/NF-κB, and upregulate PD-L1, thereby facilitating immune escape, invasiveness, and tumor progression. This review, based on a comprehensive search of Google Scholar, PubMed, and SID databases up to 2025, summarizes the role of EBV and its circRNAs in the initiation and progression of nasopharyngeal carcinoma.

Keywords: "Nasopharyngeal carcinoma, "Epstein–Barr virus", circRNA", "circRPMS1".

Introduction
Nasopharyngeal carcinoma is an uncommon malignant tumor of the upper respiratory system that develops from the epithelium of the posterior nasal cavity and upper pharynx. Unlike other head and neck cancers, the incidence of this tumor is quite low in Europe and the United States [1]. While it is substantially more common in Southeast Asia, southern China, the Middle East, and some parts of North Africa [2]. Nasopharyngeal cancer has a low frequency in Iran, with few occurrences reported. However, because of the late detection in advanced stages and the high metastatic potential, this malignancy can cause severe death. This heterogeneous geographical pattern is mainly attributed to the interaction of genetic, environmental, and infectious factors [3]. The Epstein-Barr virus (EBV) is essential in the development and progression of nasopharyngeal carcinoma (NPC). Persistent EBV infection in posterior nasopharyngeal epithelial cells causes the production of viral proteins and RNAs such as LMP1, LMP2, and EBER. This mechanism increases cellular signaling pathways, including NF-κB, PI3K/AKT, and JAK/STAT, which promote malignant cell survival. Epigenetic changes, such as hypermethylation of tumor suppressor genes and deregulation of immunological mediators, can contribute to disease progression [4]. Because of the tumor's great radiosensitivity, the conventional treatment for NPC is radiation coupled with concomitant chemotherapy. Recent breakthroughs, however, have focused on the development of targeted treatments and immunotherapies, notably PD-1/PD-L1 axis inhibitors, which have the potential to increase antitumor immune responses and patient outcomes. Furthermore, circular RNAs (circRNAs), a unique type of non-coding regulatory molecules, have lately received a lot of interest. These covalently closed RNA structures, which lack a 5' cap and a 3' tail, are exceptionally stable within cells and serve a variety of regulatory activities. They can, for example, operate as microRNA sponges, preventing gene silence, modulating gene transcription, and regulating protein activity via direct interactions. The study of circRNAs in EBV-associated NPC is crucial because they may give insights into unique molecular pathways of carcinogenesis, act as diagnostic or prognostic biomarkers, and uncover possible therapeutic targets [5]. Thus, the purpose of this study is to investigate the involvement of circRNAs in EBV-associated nasopharyngeal cancer, with an emphasis on the underlying molecular processes.

Methods
To conduct this review, data and relevant articles were systematically searched in the SID, Irandoc, Magiran, Google Scholar, Web of Science, PubMed, and Scopus databases up to 2025. Keywords used included: circular RNAs, nasopharyngeal carcinoma, Epstein–Barr virus, molecular mechanisms, clinical perspectives. The retrieved studies covered a range of basic and clinical research that investigated the role of circular RNAs in nasopharyngeal carcinoma, their association with Epstein–Barr virus infection, and the molecular pathways involved in these molecules.

Nasopharyngeal carcinoma
The first published autopsy report of a malignant nasopharyngeal tumor was in 1901 by a pathologist named Pearson William Hooper in Hong Kong. Nasopharyngeal carcinoma is a malignant epithelial tumor that originates in the posterior part of the nasal cavity and upper pharynx and is most commonly reported in Southeast Asia, particularly among the Cantonese population of Guangdong, China [6, 7]. The tumor cells of this carcinoma are typically epithelial in nature, possessing large nuclei with prominent nucleoli and exhibiting variable morphology. In the non-keratinizing form, extensive infiltration of lymphocytes and inflammatory cells within the tumor tissue is observed, producing a

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lymphoepithelioma-like appearance, whereas the keratinizing form, which is less common, is characterized by layers and plaques of keratin. The tumor architecture often consists of clusters and nests of cells, lacking a well-defined boundary with the surrounding healthy tissue [8]. Clinically, nasopharyngeal carcinoma is often asymptomatic in its early stages, but as the disease progresses, patients may develop a neck mass caused by enlarged lymph nodes, epistaxis, blood in saliva, diplopia, hearing loss, tinnitus, nasal congestion, headache, sore throat, recurrent ear infections, and facial numbness [9]. The rate of concomitant distant metastases in native patients has been found to range between 6% and 8%. Combining therapy with high-dose local chemotherapy and radiotherapy can improve overall survival in patients with newly metastatic nasopharyngeal carcinoma, and local therapy is also used in metastatic stages to reduce primary tumor volume, control metastases, and relieve symptoms [10].

Factors in Nasopharyngeal Carcinogenesis

In addition to the critical involvement of the Epstein-Barr virus in the development of nasopharyngeal carcinoma, various lines of evidence have shown the relevance of genetic and somatic changes in this illness. Candidate gene studies have revealed that MHC class I genes, such as *HLA-A*, *HLA-B*, and *HLA-C*, are most significantly related to the chance of getting this cancer [11, 12]. Furthermore, somatic changes in its major regulatory gene, *NLRC5*, have been found in around 30% of patients, which are linked with a poor prognosis. These changes enable Epstein-Barr virus-infected cells to evade host defense by altering the antigen presentation pathway [13, 14]. On the other hand, acquired mutations and genetic alterations play a crucial role in the initiation and progression of this carcinoma. Specifically, deletion or promoter methylation of *p16* has been observed in nearly all cases of nasopharyngeal carcinoma, leading to disruption of cell cycle regulation and facilitating persistent Epstein–Barr virus infection [15]. Moreover, methylation and mutations of *RASSF1A* are associated with genomic instability [16]. In addition, novel fusion genes such as *UBR5–ZNF423* and *FGFR3–TACC3* have been identified, which possess oncogenic potential and may represent promising therapeutic targets in the future [17, 18].

Epstein-Barr virus

Epstein-Barr virus is a herpesvirus with a double-stranded DNA genome that infects B-lymphocytes and spreads predominantly through saliva. The virus was initially described in 1964, and it is expected that more than 95% of individuals globally will be infected at some time in their life. The virus can cause infectious mononucleosis [19]. After entering the body, it reaches B lymphocytes and epithelial cells via surface receptors and, by triggering alterations in B lymphocytes, turns some of them into memory cells. It then stays dormant in the body until awakened under particular conditions. The most important method of transmission is close oral contact and sharing of infected food or utensils; however, it has also been recorded through transplantation or blood products [20]. Almost the entire adult population of the globe is infected with this virus, while the distribution of infection varies by age and geography. For example, in Iran, around 81% of persons carry Epstein-Barr virus IgG antibodies, with this rate increasing to more than 95% in those over the age of 40. In China, more than half of children are infected by the age of three, and the figure rises to more than 90% by the age of nine [21]. Clinical manifestations may be asymptomatic or accompanied by signs such as fever, fatigue, sore throat, and enlargement of lymph nodes and the spleen [22]. Diagnostic methods are primarily based on serological tests, including VCA-IgM and VCA-IgG [23]. There is no specific treatment for this virus, and supportive care constitutes the mainstay of patient management; however, corticosteroids may be used to control complications in severe cases. The overall prognosis is favorable, and most patients recover, although prolonged fatigue is considered the most common residual complaint [24].

Mechanisms of Epstein–Barr virus carcinogenesis in nasopharyngeal carcinoma

This virus infects nasopharyngeal epithelial cells and B lymphocytes at the same time. The virus's ability to remain and spread throughout the human body is guaranteed by the infection cycle between these two cell types. Epstein-Barr virus triggers cell division in B lymphocytes by binding to the gp350 protein of the CD21 receptor, also known as complement receptor type 2. In primordial epithelial cells, this binding is less strong, and infection often does not result in immortalization or cell proliferation. Nonetheless, Epstein-Barr virus has been found to be present in precancerous epithelium and nasopharyngeal lesions, together with the expression of lytic genes, viral cycle genes, and an elevated host antibody response, indicating a potential involvement for the virus in the early phases of carcinogenesis [25]. The entry of the virus into nasopharyngeal epithelial cells requires direct cell-to-cell contact, and receptors such as Neuropilin 1 and non-muscle myosin heavy chain IIA have been identified as mediators of viral entry into epithelial cells. Furthermore, it has been demonstrated that glycoprotein B interacts with Neuropilin 1 to facilitate internalization and fusion, while non-muscle myosin heavy chain IIA interacts with the glycoprotein H/L complex, enabling the virus to penetrate the epithelium [26]. Following viral penetration, two mechanisms for latent or lytic infection are initiated. During latent infection, several genes are active, including latent membrane proteins 1 and 2, Epstein-Barr virus nuclear antigen 1, and virus-encoded RNAs. These genes control key cellular signaling pathways, such as nuclear factor kappa B, Janus kinase/signal transducer and activator, and phosphatidylinositol-3-kinase. Latent membrane protein 1 activates nuclear

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factor kappa B, which boosts cell survival gene expression and interleukin 6 synthesis, stimulating the transcription factor 3 pathway and promoting cancer cell development. Nuclear factor kappa B also suppresses the virus's lytic cycle, stabilizing latent infection. Mutations in inhibitors of this pathway are seen in about 40% of nasopharyngeal patients, causing prolonged activation and replacing the high expression of latent membrane protein 1 [27]. Epigenetic changes are one of the most important elements of Epstein-Barr virus (EBV) oncogenesis. The virus silences tumor suppressor genes such *p16, RASSF1A*, and *CDH1*by activating DNA methyltransferases and modifying chromatin structure, affecting cell cycle regulation, DNA repair, and apoptosis [28, 29]. Furthermore, viral non-coding RNAs, such as EBERs and BART microRNAs, affect signaling pathways and help to inhibit the host immune system [30]. EBERs prevent cell death by decreasing eIF2α phosphorylation and increasing inflammatory cytokine production via Toll-like receptor 3 activation. BART microRNAs, on the other hand, shield infected cells against natural killer cell and cytotoxic T-cell assaults by inhibiting major histocompatibility complex class I molecules and cellular stress factors [31]. Epstein–Barr virus can induce cancer stem cell-like properties in nasopharyngeal cells. Latent membrane proteins 1 and 2A increase the expression of stemness markers such as CD44, SOX2, BMI1, and OCT4 by activating the Hedgehog, PI3K/AKT, and NOTCH3 pathways. These changes result in increased resistance to chemotherapeutic drugs, increased ability to form cell spheres, and redifferentiation in in vitro models and xenografts. Cells with these stemness properties typically have higher viral loads and overexpress latent genes such as EBER1 and latent membrane protein 1, suggesting a direct link between latent virus infection and stemness-like properties [32, 33].

Circular RNAs (circRNAs)

CircRNAs are a class of non-coding RNAs that, instead of having a linear structure like mRNAs, form a covalently closed loop through a head-to-tail junction. This circular configuration renders circRNAs devoid of a 5′ cap and a 3′ polyadenylated tail, making them more resistant to degradation by nucleases and therefore more stable than linear RNAs [34]. These RNAs were first identified in the Sendai virus, a murine respiratory virus, and later in plant pathogenic viruses known as viroids. The first physical evidence for the existence of circular RNAs was obtained in 1979 using electron microscopy in the cytoplasmic fraction of eukaryotic cells, HeLa cells, and later in 1986 in the HDV virus. Viral genomes with a circular structure possess a unique feature that enables them to efficiently produce multiple RNA copies and enhance infection propagation through the “rolling circle” replication mechanism [35]. In the back-splicing process, a downstream 5′ splice donor site is joined in reverse orientation to an upstream 3′ splice acceptor site, resulting in the formation of a closed, covalently continuous molecule arranged in a head-to-tail configuration, known as circRNA. Owing to their circular structure, these molecules are protected from degradation by nucleases and exhibit greater stability than linear RNAs. Moreover, by altering the order of genomic information, circRNAs contribute to increased diversity in gene expression within eukaryotic cells [36].

Mechanisms of action of circRNAs in cancer

These RNAs are able to regulate multiple cellular pathways and play an important role in cancer. One of the main mechanisms is the recruitment and inhibition of microRNAs; by this function, circRNAs block the activity of miRNAs that normally target tumor suppressor genes, resulting in increased expression of oncogenic genes. In addition, circRNAs can alter mRNA stability and translation by binding to RNA-binding proteins and activate pathways related to proliferation and survival [37].

Several studies on thyroid malignancies have demonstrated that upregulation of circ_0025033 promotes cellular proliferation and invasion by sequestering miR-1231 and miR-1304 [38]. Some circRNAs even possess the ability to encode short peptides that directly enhance pre-oncogenic pathways [39]. Furthermore, circRNAs can protect cells from programmed cell death by inhibiting pro-apoptotic proteins or activating anti-apoptotic genes. In fact, these molecules form complex interaction networks with miRNAs, proteins, and mRNAs, resulting in increased proliferation, apoptosis resistance, and cancer progression. Consequently, circRNAs have attracted significant attention as potential therapeutic targets and cancer biomarkers [40]. For instance, in pancreatic cancer, exosomal circ-IRAS has been shown to enhance cellular permeability and metastasis by downregulating miR-122 and ZO-1 while upregulating RhoA, RhoA-GTP, and F-actin [41].

The role of some non-coding RNAs in nasopharyngeal cancer

Despite the use of various treatment methods such as radiotherapy, surgery, and different treatment combinations, as well as the benefits of chemotherapy combined with radiotherapy in advanced stages, some patients still do not have a favorable prognosis. This is mainly due to the late detection of the disease, local recurrence, and the development of distant metastases. In addition, the resistance of cancer cells to radiotherapy is one of the main challenges in treatment. Side effects caused by treatment, such as upper gastrointestinal problems and bone marrow suppression, reduce patient tolerance and ultimately lead to a decrease in quality of life and limit the life expectancy of patients. With progress in understanding tumor biology, the interaction between the virus and the host cell, and genetic factors, new avenues have opened for the development of targeted therapies. Therefore, a deeper understanding of the molecular mechanisms and characteristics of the

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disease is essential for designing efficient therapeutic approaches [42]. One of the main focuses of modern research in this field is non-coding RNAs, including miRNA, lncRNA, and circRNA. These molecules regulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels, forming a complex network of molecular interactions that influence processes such as proliferation, migration, metastasis, and drug resistance in nasopharyngeal cancer [43].

MicroRNAs (miRNAs) are short RNA molecules, typically 19 to 25 nucleotides in length, that regulate gene expression by binding to the 3′ untranslated region (3′-UTR) of target mRNAs, thereby inhibiting translation or promoting mRNA degradation. Depending on their functional role, miRNAs can act either as tumor suppressors or oncogenes. Notably, EBV is the first identified human virus capable of encoding specific viral miRNAs. These miRNAs are abundantly expressed in infected cells and play crucial roles in maintaining viral latency, modulating host gene expression, and facilitating immune evasion by the virus. Research evidence suggests that EBV-encoded miRNAs can target the expression of host mRNAs involved in processes such as cell proliferation, apoptosis, and cellular phenotype change. Furthermore, by inhibiting the expression of viral antigens, these miRNAs prevent infected cells from being recognized by immune cells, thereby contributing to the virus's escape from the immune response [44].

Long non-coding RNAs (lncRNAs), which are longer than 200 nucleotides, are predominantly expressed in the nucleus and participate in various biological processes such as chromatin remodeling, splicing, translation, and mRNA stability through interactions with DNA, RNA, or proteins. In nasopharyngeal carcinoma (NPC), many lncRNAs exhibit altered expression levels, with some, such as MEG3, LET, and LINC0086, functioning as tumor suppressors. Downregulation of these lncRNAs promotes enhanced proliferation, cell migration, and treatment resistance [45]. For instance, MEG3 is often silenced by promoter hypermethylation or gene deletions, and its re-expression can inhibit cell growth, induce apoptosis, and reduce tumorigenicity.

Many of these molecules act as miRNA sponges, thereby modulating key regulatory pathways. For example, lncRNAs such as NEAT1 and XIST regulate miRNA–mRNA axes, including miR-34a-5p, which play critical roles in controlling cell growth and resistance mechanisms. Recent studies have demonstrated that EBV infection can modulate these regulatory pathways either through its own viral miRNAs or by altering the expression of host lncRNAs such as NEAT1 and XIST ultimately enhancing tumorigenesis and promoting the survival of infected cells [46].

circRNAEpstein–Barr virus in association with nasopharyngeal carcinoma

The virus (EBV/HHV-4) is the first virus identified to produce circRNA in its genome. This oncogenic virus has a large DNA genome (~172 kb) containing over 80 ORFs, several miRNAs, and long non-coding RNAs.In recent years, researchers have applied RNA sequencing to total RNA from EBV-positive cell lines, such as SNU-719, AGS-EBV, C666-1, and Akata, identifying a repertoire of viral circular RNAs .One of these molecules, ebv_circ_RPMS1, was observed in both the nuclear and cytoplasmic compartments. After infection, the circular EBV genome persists in the host cell nucleus as an episome, interacting with viral proteins and associating with host chromosomes [47]. These episomes are methylated, chromatinized, and transmitted to daughter cells, and can be considered analogous to additional chromosomes when analyzing viral transcripts. The number of episomes per cell varies and depends on the phase of the viral life cycle, including latent and lytic phases [47]. Additionally, Toptan et al. reported the presence of a set of viral circRNAs, referred to as circBARTs, across all EBV latency types, including in nasopharyngeal carcinoma cells. These findings indicate that circBARTs likely play a key role in viral oncogenesis and in maintaining EBV infection [48]. Studies have shown that these viral circRNAs are derived from transcripts of the BART and RPMS1 regions of the virus and contribute to the development and progression of nasopharyngeal cancer through several molecular pathways. One of the most important mechanisms is the sponging of cellular microRNAs. CircRNAs such as circRPMS1 have sequences that are complementary to, and trap, host tumor suppressor miRNAs such as miR-203, miR-31, and miR-451. As a result, these miRNAs cannot repress their target mRNAs, and the expression of proto-oncogenes is increased [49].

In 2019, a study investigated the role of the Epstein–Barr virus-derived circular RNA, circRPMS1, in nasopharyngeal carcinoma. Using patient tissue samples along with in vitro and in vivo experiments, the researchers evaluated the impact of this molecule on cell proliferation, apoptosis, invasion, and metastasis. The results demonstrated that circRPMS1 levels were elevated in metastatic tumors and correlated with reduced patient survival. Knockdown of circRPMS1 inhibited cell growth, promoted apoptosis, and reduced cellular invasion in EBV-infected cells. Furthermore, it was found that circRPMS1 contributes to tumorigenesis by sponging multiple miRNAs and promoting epithelial–mesenchymal transition [50]. In addition, some studies have shown that a viral circRNA can interact with cellular RNA recognition proteins, such as RIG-I, and alter immune signaling pathways. As a result, the transcription of certain immune response regulatory genes, such as PD-L1, is increased, enabling the tumor to gain immune evasion. Ge et al., in a comprehensive study, showed that circBART2.2, encoded by the BART region of the virus, binds to RIG-I and leads to increased PD-L1 transcription in NPC cells through

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the activation of the IRF3/NF-κB pathways, providing a clear mechanism for tumor immune evasion [51]. EBV also suppresses the tumor immune environment by increasing B7-H3 expression and impairing NK cell function, combined with immunoregulation by circRNAs. Metabolomic studies and animal models have also shown that EBV can keep circRNA-related pathways active and promote NPC malignancy progression through stimulation of glycolysis and lipid metabolism [18].

Circular RNAs are capable of interacting with RNA-binding proteins (RBPs) and transcription factors, forming complex molecular assemblies. These interactions can influence mRNA stability, translation efficiency, and the activity of signaling factors, thereby modulating key cellular pathways such as NF-κB, JAK/STAT, and those associated with cell survival and apoptosis. Evidence from viral studies indicates that EBV-derived circRNAs can directly interact with RBPs, and several reviews and research articles have detailed the mechanisms involved in RBP–circRNA interactions in oncogenic processes [52]. In addition, circRNAs can be packaged into exosomes and transferred between cells. Through this mechanism, their cargo including viral or host circRNAs can reprogram neighboring cells, such as fibroblasts, immune cells, or endothelial cells, thereby remodeling the tumor microenvironment to favor tumor growth and survival. Extensive evidence suggests that circRNAs are stable within exosomes and can function as mediators of intercellular signaling. Multiple studies in nasopharyngeal carcinoma have demonstrated that exosomes can induce treatment resistance, maintain stemness features, and promote immunosuppression [53]. For example, research indicates that exosomal circPARD3 can enhance stemness and cisplatin resistance in EBV-miR-BART4-induced side population NPC cells. In the cancer tissues and cell lines, circPARD3 was upregulated along with SIRT1 and SSRP1, while miR-579-3p was downregulated. CircPARD3 exhibited a positive correlation with SIRT1 and SSRP1 and a negative correlation with miR-579-3p. The function of exosomal circPARD3 is mediated through the miR-579-3p/SIRT1/SSRP1 axis: miR-579-3p reverses the effects of circPARD3, SIRT1 enhances SSRP1 expression via H3K4 methylation, and SSRP1 suppression counteracts the SIRT1-mediated induction of stemness and resistance. These findings suggest that the transfer of circRNAs via exosomes can prime the tumor microenvironment to support NPC cell growth and therapeutic resistance [54].

Furthermore, some circRNAs contain open reading frames (ORFs) and start sites, as well as m^6A or internal ribosome entry sites (IRES), enabling the translation of short peptides (circRNA-encoded peptides). These peptides may possess novel signaling activities that contribute to apoptosis suppression or activation of growth-promoting pathways [55].

Functional differences between viral and host circRNAs in nasopharyngeal carcinoma

Although circRNAs derived from the host genome and circRNAs derived from viruses both play a role in regulating gene expression, cellular stability, and controlling immune responses, they have many differences in structure, pathways of action, and biological consequences, including the greater stability of EBV-derived viral circRNAs. In fact, these circRNAs have the property of evading host immunity and promoting the survival of infected cells [56]. Moreover, these circRNAs, through their miRNA sponge function, can directly interact with host nuclear proteins, leading to epigenetic reprogramming that creates a favorable environment for the proliferation and immortalization of infected epithelial cells [57].

Another distinctive feature of viral circRNAs is their dual role in latent and lytic infection. Specifically, viral circRNAs alter their expression in response to cellular stress, lytic induction, or anticancer treatments. This adaptive expression highlights their active participation in the viral life cycle and the ability of cancer cells to adjust to the microenvironment [58].

Conclusions

Epstein-Barr virus is one of the causative agents that plays a fundamental role in the development and progression of this malignancy by creating a complex interaction between the viral genome and the host cell. Studies on viral and host circRNAs have provided cancer researchers with a new perspective in understanding the molecular mechanisms of this malignancy. These circRNAs not only play a role in regulating the expression of key genes and signaling pathways, but also contribute to the creation of a treatment-resistant environment through interactions with miRNAs, proteins, and exosomes. In addition, the expression of many viral circRNAs, such as circRPMS1 and circBART2.2, is associated with progression, metastasis, and poor prognosis in patients with malignancy, and they can be used for early diagnosis of this malignancy and assessment of treatment response.

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