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Epstein-Barr Virus Participates in the Development and Progression of Nasopharyngeal Carcinoma and its Application in Traditional Chinese and Western Medicine Integrated Treatment

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Abstract: Nasopharyngeal carcinoma (NPC) is a epithelial tumor from the nasopharynx. Its pathogenesis is closely related to Epstein-Barr virus (EBV) infection, the patients account for over 95% of global NPC incidence. NPC is a highly malignant tumor, with over 70% of patients diagnosed at an intermediate or advanced stage. Over 90% of those diagnosed with undifferentiated NPC are infected with EBV. Currently, radiotherapy alone and concurrent chemoradiotherapy are the main treatment options for NPC. Early-stage NPC is primarily treated with radical radiotherapy, appropriately combined with chemotherapy, while locally advanced NPC is treated with concurrent chemoradiotherapy. However, long-term radiotherapy and chemotherapy can be difficult for NPC patients and can cause corresponding toxic side effects. Therefore, tumor immunotherapy is a promising treatment method for NPC, including vaccination, adoptive cell therapy, and immune checkpoint blockade. In addition, traditional Chinese medicine treatment can improve the immune status of NPC patients, reduce the toxic side effects of radiotherapy and chemotherapy, and improve survival time and quality of life. Therefore, the traditional Chinese and Western medicine treatment for NPC patients has shown remarkable efficacy; this also suggests that the traditional Chinese and Western medicine treatment of NPC has broad development prospects. Herin, we summarize mechanisms of EBV involved in NPC, and mainly elaborate the traditional Chinese and Western medicine treatment targeted EBV for NPC patients. This article provides some insights for future related research.

Keywords: Epstein-Barr virus; Nasopharyngeal carcinoma; Traditional Chinese medicine; Integrated treatment of traditional Chinese

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Introduction

Nasopharyngeal carcinoma (NPC) is a highly invasive head and neck malignant tumor originating from epithelial cells of nasopharyngeal mucosa. In high-incidence areas, more than 95% of nasopharyngeal carcinoma incidence is attributed to Epstein-Barr virus (EBV), a ubiquitous virus that causes lifelong asymptomatic infection in most populations worldwide[1, 2]. Common tumors associated with EBV infection include NPC, primary pulmonary lymphoepithelial carcinoma (PLELC), EBV-associated intrahepatic cholangiocarcinoma, and EBV-associated gastric cancer (EBVaGC) [3–7]. NPC accounts for up to 80 % of these tumors, and more than 90% of NPC patients have EBV infection[8, 9]. According to the latest global cancer statistics released by the International Agency for Research on Cancer (IARC) in 2022, the global incidence of NPC is estimated at 120,416 cases and the number of deaths is 73,476. The patients in Asia account for 83.3% (100,298 cases) of global NPC incidence and 83.6% (61,442 cases) of deaths. East Asia, southeast Asia, and central and south Asia are the endemic areas, and China has the highest incidence, at about 2.4/100,000 people/year (51,010 cases)[10]. NPC has a relatively hidden location and is sensitive to radiotherapy.

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Its clinical treatment is mainly radiotherapy, and chemotherapy can be combined for locally advanced stages . According to the latest CSCO guidelines for the treatment of head and neck tumors, concurrent chemoradiotherapy for NPC has good effects. The main treatment options are concurrent chemoradiotherapy, induction chemotherapy, and adjuvant chemotherapy. For patients with early-stage NPC, radiotherapy alone or combination therapy is the main treatment method [11, 12]. For locally advanced NPC, the main treatment modes have concurrent chemoradiotherapy, induction chemotherapy followed by concurrent chemoradiotherapy, and concurrent chemoradiotherapy followed by adjuvant chemotherapy. Although the combined chemoradiotherapy can improve the prognosis of patients with NPC, its efficacy is limited, and about 8-10% of patients still have experience recurrence or metastasis in the later stages [13–15]. Moreover, long-term concurrent chemoradiotherapy can lead to complications, such as dry mouth, trismus, and secondary tumors, which seriously affect the life quality of patients[16-20]. EBV infection is closely related to NPC, which makes EBV become a key target for tumor treatment. Immune cell infiltration and EBV antigen expression in NPC patients are the main research targets of immunotherapy [21, 22]. Traditional Chinese medicine has significant advantages in cancer treatment, with characteristics, such as reduced toxicity and enhanced efficacy, flexible formulation, and significant curative effect. Traditional Chinese medicine treatment not only prolongs disease-free survival but also reduces complications and adverse reactions associated with radiotherapy and chemotherapy, demonstrating significant clinical value. Here, we summarize research progress in the field of EBV and its relationship to NPC development and progression, as well as important research findings on the integration of traditional Chinese medicine in the treatment of NPC patients. This article provides promising directions for future research on NPC treatment.

Biological Characteristics of EBV

Isolated from the cells of a Burkitt lymphoma (BL) patient in Africa [23, 24], primary EBV infections are asymptomatic, with more than 95% of adults worldwide infected. It is mainly transmitted through bodily fluids, and its host cells mainly include epithelial cells and B cells. EBV causes as many as 200,000 deaths annually [25, 26]. EBV-induced diseases are mainly caused by an imbalance between the virus and the body's immune system after infection, which drives the host cells to undergo malignant transformation and cause disease. EBV is a herpesvirus with a bidirectional life cycle, including a latent phase and a replication phase [27]. The latent phase is mainly established after the host cells are infected with the virus. During this period, viral particles cease to be produced, and only a few essential viral genes are expressed [1, 28, 29]. EBV encodes eight latent genes, and naive B cells infected with EBV exhibit a latent phase III. Latent phase III genes include six EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, LP), two latent membrane proteins (LMP1 and LMP2), EBV-encoded small RNAs (EBERs), and EBV-encoded microRNAs (miRNAs) [30]. The cells in this latent phase are highly immunogenic and can be rapidly captured by the host's EBV-specific T cells [31]. However, the "true latent phase" shows that in most individuals, EBV persists in a subset of memory B cells without expressing any viral genes in the latent phase 0 state [32]. Latent EBV genes can promote tumorigenesis, inhibit apoptosis, and suppress the recognition of infected cells by host immune cells [30]. After entering B cells, the viral genome usually exists in the nucleus in the form of circular fragments [33]. EBV latent proteins are generally considered to be key drivers of tumorigenesis in EBV-associated tumor. EBNA1 is a transcription factor that is essential for the maintenance and replication of EBV in vitro [34]. Similarly, EBV that knocks out EBNA1 loses its ability to latently infect cells in vitro. EBNA1 can upregulate proteins to involve in metastasis and oxidative stress in EBV-positive NPC cells [35]. EBNA1 is also the only EBV protein that is consistently expressed across all latent phases, making it become a key target for EBV-specific therapy in all EBV-associated tumors. The studies have shown that inhibiting EBNA1 can effectively suppress the proliferation of EBV-positive tumor cells [36]. EBNA2 is a transcriptional activator of cellular genes (such as CD21, CD23, and c-MYC) and viral genes (such as LMP1 and LMP2). LMP1, encoded by EBV, is an essential membrane protein. LMP1 mimics the cell CD40 receptor and is a member of the (TNFR) superfamily. It can drive the growth and differentiation of B cells by replacing the function of CD40 in vivo [37]. The LMP1 signaling pathway is mainly mediated by the interaction of host TNFR-related factors (TRAFs) or death domain protein TRADD with CTAR1 or CTAR2 to promote the activation of upstream regulators of multiple signaling pathways [38]. LMP1 is an oncogene of EBV and is crucial for the in vitro transformation of B cells. As a CD40 receptor, LMP1 affects the expression of cytokines such as IL-6 and IL-8, regulates immunity, and influences tumor cell proliferation, metastasis, and invasion by activating the NF-κB pathway [39] .

EBV and Tumorigenesis

EBV is associated with a variety of diseases and malignancies. For example, infectious mononucleosis (IM) is associated with primary EBV infection. Chronic active EBV infection (CAEBV), although rare, is life-threatening and is characterized by an abnormally high EBV DNA load [40]. EBV is also a major risk factor for immunocompromised patients. In HIV patients, the lack of antibodies that can effectively respond to EBV-specific T cells significantly increase the risk of developing EBV-related lymphoma [41, 42]. Post-transplant lymphoproliferative disorder (PTLD) is associated with the reactivation and replication of EBV in most cases [43]. EBV infection is also associated with the development of autoimmune diseases such as multiple sclerosis (MS) [44]. The incidence of EBV-related malignancies is slightly higher in men than in women [45]. In addition, EBV infection is associated with a variety of lymphomas, including Burkitt lymphoma (BL), Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), NK/T-cell lymphoma and primary effusion lymphoma [46], and epithelial malignancies including NPC and GC. The

mechanisms of EBV-induced NPC were discussed in more detail below.

The Relationship between EBV with NPC Occurrence and Development

EBV infection is a key-risk factor for the development of NPC, and It plays an important role in NPC progression [47]. About 90% of malignant cells in NPC are undifferentiated or poorly differentiated squamous epithelial cells that typically express several EBV latency type II gene products [48]. These genes include EBER1/2, EBNA1, LMP1, LMP2, BARF1, and several other non-coding transcripts encoded by EBV. LMP1 is one of the key oncogenic drivers of NPC development, expressed in 20–60% of NPC and all precancerous or preinvasive lesions, and has become a major therapeutic target [49]. More than 50 mutations were found in each of 111 microscopically dissected EBV-positive tumor samples. Whole exome sequencing of NPCs has revealed a series of key cellular pathway gene mutations, including p53, HLA, NF-κB, MAPK and PI3K [50]. About 90% of EBV-positive NPCs have NF-κB inflammatory pathway activation characteristics, which may be due to somatic mutations or the expression of the LMP1 oncogene encoded by EBV [51]. LMP1 is usually expressed in NPC cells, and it can inhibit DNA repair in human epithelial cells through the c-terminal activation region 1 (CTAR1). The PI3K/Akt pathway is involved in LMP1-mediated DNA repair inhibition. DNA damage binding protein (DDB1) is involved in nucleotide excision repair. The LMP1/PI3K/Akt pathway can inactivate FOXO3a, inhibit DDB1 expression, and lead to genomic instability in human epithelial cells [52]. In addition, the weakened immune system of NPC patients is an important cause of its pathogenesis, and EBV has a variety of ways to evade the host's immune system attack. EBV infection and expression of various lysed EBV gene proteins may block the secretion of various antiviral cytokines. For example, EBV immediate early lysation proteins, including BZLF1 and BRLF1, inhibit the production of interferon response genes and type I interferon [53]. Lysed EBV proteins may also affect the host's innate immunity through interfering with intracellular NF-κB signaling by regulating TLR expression on the surface of virus-infected cells. Potential EBV gene products also play a role in regulating the host's immune response. The EBV-encoded gene product EBER is expressed at high levels in all latent EBV infections, and can inhibit interferon-stimulated gene activity by binding to double-stranded RNA-dependent protein kinase PKR [54]. EBV-infected cells can secrete exosomes to regulate immune activity [55, 56]. These exosomes have been shown to contain LMP1, galactoglobulin 9, and other immunomodulatory molecules, which may regulate the function of immune cells in NPC microenvironment [56]. LMP2A and LMP2B, encoded by EBV, inhibit type I IFN responses in epithelial cells by disrupting IFN-stimulated gene transcription and targeting IFN receptor degradation [57]. EBV-encoded miRNAs play an important role in immune evasion [58]. EBV-encoded BART-miRNAs are highly expressed in NPC cells. Cellular targets of BART-miRNAs identified in immune evasion include major histocompatibility complex class I related chain B (MICB). Decreased expression of MICB on the cell surface leads to a reduced cytolysis response following NKG2D activation, enabling EBV-infected cells to evade immune detection [59].

NPC Integrated-Treatment with Traditional Chinese

Because the onset of NPC is hidden, its clinical treatment is often based on radiotherapy. However, according to the latest CSCO treatment guidelines, the status of concurrent chemoradiotherapy for nasopharyngeal carcinoma has gradually increased. The main treatment strategies include concurrent chemoradiotherapy, induction chemotherapy, and adjuvant chemotherapy, their clinical efficacy is good. The patients with early and mid-stage NPC are mainly treated with radiotherapy or combined chemotherapy. NPC patients at Stage I (T1N0) is often treated with radiotherapy alone, and intensity-modulated radiotherapy (IMRT) is strongly recommended [60]. The treatment options for stage II NPC (T1N1/T2N0-1) are quite controversial. Concurrent chemoradiotherapy has certain advantages, but it is limited to two-dimensional irradiation techniques [61, 62].

Several retrospective studies have shown that radiotherapy alone using IMRT technology has a good therapeutic effect on intermediate NPC, but for patients with a high incidence of distant metastasis (T2N1), concurrent chemoradiotherapy seems to be more effective [63–65]. There are also prospective randomized controlled studies that have shown that for patients with stage II NPC, there is no difference between IMRT and concurrent chemoradiotherapy in overall survival terms, local control, or distant metastasis [66]. For low-risk stage II and stage III (T3N0M0) patients, there is no difference between IMRT and concurrent chemoradiotherapy on the primary endpoint of 3-year failure-free survival, while the results of secondary endpoints such as overall survival, local recurrence, and distant metastasis are still immature [67]. Concurrent chemoradiotherapy should be used for locally advanced NPC, cisplatin is the most commonly used drug [68, 69]. Randomized studies have shown that patients treated with weekly cisplatin regimens have a higher incidence of myelosuppression and hearing impairment [70–75]. For the patients who are intolerant to cisplatin, nedaplatin, carboplatin, etc. can be used as alternative treatments. For patients who are intolerant to chemotherapy, radiotherapy combined with cetuximab or nimotuzumab can be chosen. Although there is a lack of relevant randomized controlled trials [76], nimotuzumab significantly improved 5-year overall survival without significantly increasing toxicity when combined with concurrent chemoradiotherapy with cisplatin [77]. Induction chemotherapy followed by concurrent chemoradiotherapy is another treatment modality for locally advanced NPC. Previous meta-analyses have shown that induction chemotherapy helps improve local control, but does not improve overall survival [78, 79].

However, in two recent prospective randomized controlled trials of locally advanced NPC (excluding T3-4 N0), three cycles of the GP regimen or the modified TPF regimen significantly improved various endpoints, including overall survival, on top of concurrent chemoradiotherapy with IMRT and cisplatin [18, 80–82]. Concurrent chemoradiotherapy followed by adjuvant chemotherapy is another treatment option for locally advanced NPC, but previous studies have suggested that the completion rate is not ideal due to radiotherapy toxicity. Although the early randomized studies suggested that this mode could improve overall survival compared to radiotherapy alone, it cannot be ruled out that the benefit mainly comes from concurrent chemoradiotherapy [70–72]. The subsequent two randomized controlled trials using PF and GP regimens as adjuvant chemotherapy respectively had negative results, with the latter being more targeted at high-risk patients with residual EBV DNA after radiotherapy [83–85]. A prospective randomized controlled trial of capecitabine metronid chemotherapy showed improvement in all endpoints, including 3-year overall survival, and the benefit was independent of whether or not induction chemotherapy, but the results still need to be verified by long-term follow-up [86]. Two other prospective randomized controlled trials in patients with locally advanced disease who received concurrent chemoradiotherapy showed that 8 cycles of conventional capecitabine chemotherapy or 3 cycles of GP regimen could improve 3-year failure-free survival or progression-free survival [77, 87]. The optimal adjuvant chemotherapy regimen, chemotherapy cycle and benefit population still need to be determined, and the relationship between this treatment modality and induction chemotherapy on the overall efficacy still needs further research.

In recent years, immunotherapy has gradually emerged in the clinical management of tumors. Immunotherapy activates immune response in the tumor microenvironment by changing the biological characteristics of immune effector cells, thereby inhibiting or killing cancer cells. Modulated immunotherapy for NPC has shown good efficacy and safety, and has become a promising treatment method. Several types of immunotherapy, including adoptive cell transfer (ACT) and ICIs, have achieved durable clinical responses, but their efficacy varies. With the rapid development of immunotherapy, drugs that target immune checkpoint inhibitors (ICIs) are widely used in various solid tumors such as lung cancer, head and neck tumors, and cervical cancer. The occurrence and development of NPC are closely related to EBV infection. Therefore, a large number of EBV antigens, including latent membrane proteins and nuclear antigen-1, which can induce antitumor activity, have been detected in NPC diagnosis and efficacy evaluation. In addition, NPC is also known as "lymphoepithelioma". The microenvironment of inflammatory tumors is assembled with immune cell infiltration, which makes it a good basis for immunotherapy. Vaccination is the most effective treatment for preventing EBV infection [88]. Recently, nimotuzumab, a humanized monoclonal antibody targeting epidermal growth factor receptor (EGFR), has come into view. Many clinical trials have shown that nimotuzumab plus chemotherapy, radiotherapy or simultaneous radiotherapy and chemotherapy have certain therapeutic effects on patients with locally advanced and relapsed or metastatic NPC [89]. In terms of cell therapy, the main treatments include chimeric antigen receptor T-cell immunotherapy (CAR-T), tumor-infiltrating lymphocyte therapy, natural killer cell therapy and cytokine-induced killer cell (CIK) therapy. Clinically, the safety and preliminary efficacy of EBV CAR-T therapy to relapsed/refractory NPC are significant [90].

Traditional Chinese medicine can improve the immune function of tumor patients, prevent recurrence and metastasis, prevent or reduce the toxicity of radiotherapy and chemotherapy and improve the quality of life of patients. The specific mechanism of most Chinese medicines is still unclear, but many Chinese medicines have been found to effectively promote and stimulate the immune system, thereby improving the immune function of NPC patients and reducing toxic reactions. Chinese medicine compound treatment for symptoms, supporting the body's resistance and eliminating pathogens, helps the body restore the balance of yin and yang, enhance the body's anti-tumor ability, and thus effectively reduces the adverse reactions that occur after radiotherapy and chemotherapy in NPC patients. Jiang, et al. thought that the effective intervention of the Chinese medicine compound Yiqi Jiedu formula can reduce the proportion and activity of CD4+ CD25+ T regulatory cells of in the patients with mid-to-late stageNPC, increase the proportion and functional activity of immune effector cells Th17, help to reverse immune tolerance phenomenon in the tumor microenvironment of NPC, and thus enhance the anti-tumor ability of NPC patients [91]. Zhang Bei, et al. observed the correlation between TCM syndrome type and clinical stage and EBV-DNA concentration in newly diagnosed NPC patients. The results showed that the lung heat type had an earlier TNM stage and low EBV-DNA concentration in the four types. The blood stasis and phlegm coagulation type were all stage III and IV patients, and the highest EBV-DNA concentration was in the four types [92]. The results suggest that there is a certain correlation between TCM syndrome type and EBV-DNA concentration in NPC patients [92]. The peripheral blood T lymphocyte subset values of tumor patients are abnormal. The characteristic is that the CD3+ and CD4+ cells in the patient's body are significantly reduced, while the CD8 + cells are significantly increased. The CD4+/CD8+ ratio is significantly reduced, showing an immunosuppressive state [92]. Li, et al. explored the correlation between four syndrome types (phlegm accumulation type, qi and blood stagnation type, body fluid deficiency type, and spleen and stomach qi deficiency type) and T cell subsets pre- and post-treatment of NPC radiotherapy and chemotherapy. The results showed that the phlegm accumulation type and qi and blood stagnation type at pre-treatment transformed into spleen and stomach qi deficiency type at post-chemotherapy, and transformed into body fluid deficiency type posy-radiotherapy [93]. The expression level of CD4+ and CD4+/CD8+ at post-treatment was significantly higher than atpre-treatment, while the expression level of CD8 + was significantly lower than that at pre-treatment. This suggests that the expression levels of CD4+ and CD8+ and the CD4+/CD8+ ratio changed significantly in different TCM syndrome types at pre- and

post-treatment of NPC patients [93]. Compared with radiotherapy alone, it combined with TCM treatment significantly reduced adverse reactions, including acute oropharyngeal mucositis and acute skin radiation reaction [94]. Gao, et al. explored the effects of radiotherapy on acute oropharyngeal mucosal reaction and immune function caused by NPC. The results showed that the TCM syndrome score, degree of oral mucosal damage, CD8+ index, saliva flow rate, and amylase secretion rate of the observation group were all lower than those of the control group after treatment. Moreover, CD3+, CD4+ and CD4+/CD8+ indexes were higher than those of the control group after treatment. The results showed that the intervention of Qingre Liyan Decoction for radiotherapy patients can effectively prevent and treat acute oropharyngeal mucosal reaction and improve immune function, which has clinical promotion value [95]. Wang, et al. explored the use of blood-activating, qi-tonifying and yin-nourishing Chinese medicine to reduce acute toxic side effects of radiotherapy. Blood-activating, qi-tonifying and yin-nourishing formula can significantly reduce acute radiation damage to mucosa and skin and bone marrow suppression [96].

NPC treatment primarily includes radiotherapy and chemotherapy. Despite significant advancements in treatment options in recent years, local recurrence or/and distant metastasis are still main factors to lead to treatment failure. EBV activates tumor lymphocyte infiltration (TIL) and increased expression of programmed death receptor 1 (PD-1) or its ligand (PD-L1), all of which could potentially become therapeutic targets. Therefore, targeting EBV and immunotherapy to PD-1/PD-L1 may be an effect therapy for NPC. East Asia, southeast Asia, and central and south Asia have the highest incidence of NPC worldwide. Etiological and pathogenesis studies show that the occurrence of NPC is related to genetic factors, and EBV also plays a crucial role. Therefore, controlling EBV infection and activation in the population and reducing the levels of various EBV antibodies may prevent NPV or reduce its incidence. 5-year survival rate for radiotherapy in NPC is generally around 45%, and the side effects are significant; a small number of patients are not very sensitive to it. Therefore, searching anti-EBV drugs with non-toxic or low-toxicity from traditional Chinese medicine is an effective way to prevent and reduce NPC incidence. Yiqi Jiedu formula has played some role in the prevention, treatment, prognosis improvement of NPC, as well as in reducing the side effects of radiotherapy, but its effect and mechanism are not clear. Conducting research on the prevention and treatment of NPC using integrated traditional Chinese and Western medicine are still an urgent and important task in future, especially those working in areas with a high incidence of NPC.

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