Immune Microenvironment of Nasopharyngeal Carcinoma and Epstein-Barr Virus

Subjects: Oncology

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Reports about the oncogenic mechanisms underlying nasopharyngeal carcinoma (NPC) have been accumulating since the discovery of Epstein-Barr virus (EBV) in NPC cells. EBV is the primary causative agent of NPC. EBV–host and tumor–immune system interactions underlie the unique representative pathology of NPC, which is an undifferentiated cancer cell with extensive lymphocyte infiltration. Recent advances in the understanding of immune evasion and checkpoints have changed the treatment of NPC in clinical settings. The main EBV genes involved in NPC are LMP1, which is the primary EBV oncogene, and BZLF1, which induces the lytic phase of EBV. These two multifunctional genes affect host cell behavior, including the tumor–immune microenvironment and EBV behavior.

nasopharyngeal carcinoma Epstein-Barr virus gene expression LMP1 BZLF1 immune microenvironment immune evasion

1. Histopathology of NPC and EBV Infection

EBV infection is closely associated with pathological characteristics of NPC. The World Health Organization (WHO) classification system, which is based on the grade of differentiation of tumors, is generally accepted for the pathological classification of NPC. WHO grades I, II, and III represent keratinizing, non-keratinizing-differentiated, and non-keratinizing-undifferentiated NPC, respectively. WHO II and III are considered to indicate EBV-associated NPC [1]. However, there has been a debate on the relevance of EBV in WHO I NPC diagnosis. A previous prevalent opinion was that WHO I NPC was originally an EBV-driven tumor. Throughout the tumor progression, EBV escaped or was eliminated from tumor cells. Thus, a small amount of EBV DNA was detected in WHO type I tumors. However, a recent prevalent opinion based on serological and histological studies is that WHO I NPC is a squamous cell carcinoma similar to general head and neck carcinoma.

EBV-associated WHO II and III NPCs are characterized by the prominent infiltration of lymphocytes in the tumor-surrounding area and the so-called lymphoepithelioma. This difference in histological features has been investigated in various directions regarding the association between EBV and the clinical features of NPC.

WHO I NPC accounts for less than 20% of NPC cases globally. This rate is relatively low in endemic areas, such as Southeast Asia and southern China. In other words, the prevalence of non-keratinizing (WHO II, III) NPC is

higher in endemic areas (>95%) and is predominantly associated with EBV infection. However, patients with NPC present elevated IgG and IgA concentrations in response to the viral capsid antigen (VCA) and early antigen (EA) of EBV regardless of endemic or non-endemic area [2]. For WHO I NPC, initial studies reported similar pathology and EBV serologic profiles similar to those of other head and neck carcinomas [3][4], whereas other studies have suggested that all types of NPC result in elevated concentrations of EBV antigens [5]. Recent high-resolution analyses, such as duplex multiplex assays for EBV IgA and IgG antibodies, have shown that very fine adjustment of sample sera is mandatory for the precise quantification of antibody titers [6][7]. Presumably, the mixed review of the serological association of WHO I NPC is attributable to technical problems. However, it is generally accepted that WHO I represents NPC that is unrelated to EBV, and WHO II and III represent EBV-associated NPC. The clinical characteristics of WHO I NPC differ from those of WHO II and III NPCs. A multicenter prospective trial revealed that patients with WHO I NPC had no distant metastatic recurrence, and all relapsed sites were locoregional areas. This pattern is similar to the patterns of conventional head and neck cancers. In contrast, patients with WHO II and III NPCs had significantly higher rates of distant metastatic recurrence. These results indicate that EBV contributes to the high metastatic properties of WHO II and III NPCs [8] (**Table 1**).

Table 1. Nasopharyngeal cancer histology and clinicopathological features.

	WHO I	WHO II	WHO III
Differentiation status	well differentiated	moderately to poorly differentiated	undifferentiated
Histological category in WHO classification	keratinizing	nonkeratinizing-differentiated	nonkeratinizing-undifferentiated
TIL infiltration	fair to moderate	heavy	
EBERs in tumor	(−) or faint	(+)	
EBV antibodies	not elevated	elevated	
Chemoradiosensitivity	moderate	good	
Metastatic property	low to moderate	high	
Epidemiology	20% in non-endemic area; <5% in endemic areas	80% in non-endemic areas; >95% in endemic areas	

EBERs: EBV-encoded small RNAs, TIL; tumor-infiltrating lymphocytes, WHO; World Health Organization.

Recently, human papillomavirus (HPV) infections in head and neck carcinomas, especially oropharyngeal carcinomas, have been incorporated into NPC research. HPV was detected in two of the 58 NPC tissues at our institute. The HPV-positive cases were classified as WHO II, and EBERs were detected using in situ hybridization. One case had HPV18, and the others had HPV16 and 18 [9].

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Reports have been inconsistent, likely because of the limited number of patients and the ethnic and geographic differences among the study populations. Several studies have detected HPV in NPC, with some demonstrating a dichotomy between EBV and HPV infections predominantly in non-endemic regions [10][11][12]. Others have reported cases of EBV and HPV co-infection, predominantly in patients from endemic regions [13][14][15]. Similar to EBV, a serological test has been developed for HPV and applied to screening for HPV-associated diseases [16].

EBV-associated NPC is characterized by the prominent infiltration of lymphocytes in the tumor-surrounding area and the so-called lymphoepithelioma. Based on the unique pathological features of NPC, the relationship between the immune system and NPC tumor cells has been intensively investigated.

The nasopharynx contains a unique lymphoid tissue called the nasopharynx-associated lymphoid tissue (NALT), which differs from other lymphoid tissues involved in organogenesis. NALT plays an important role in the mucosal immune system [17]. The secretion of anti-EBV IgA from the NALT into the airway lumen and serum is a marker for NPC screening and diagnosis. New insights into the tumor microenvironment of NPC have been growing, including the tumor immune microenvironment (TIME). The tumor microenvironment is mainly composed of heterogeneous cellular components such as tumor cells, fibroblasts, endothelial cells, and leukocytes. It also contains various mediators, such as cytokines and exosomes, which influence the behavior of NPC tumors and, eventually, the prognosis of NPC patients. The TIME consists of immunostimulant and immunosuppressive components. Thus, the TIME component also serves as a prognostic biomarker and a potential target for novel therapies [18].

Tumor-infiltrating lymphocytes (TIL) in NPC tissue contain various immune cells, and the proportion of the immune population dynamically changes with tumor progression and treatment. However, TIL levels usually reflect the treatment outcomes of patients. Accordingly, increased numbers of TILs are predictive markers of favorable outcomes in patients with NPC [19].

2. Immune Evasion Mechanism in NPC

Malignant tumor cells begin the construction of the TIME once they are recognized as targets of immune cells. Subsequently, the tumor cells escape the immune attack. Generally, viral proteins are presented as antigens combined with MHC class I molecules to recruit CD 8-positive cytotoxic T cells (CTL) to the virus-infected tumor cells. Three EBV genes, EBNA1, LMP1, and LMP2, are expressed in NPC. However, EBV-encoded gene products expressed in NPC cells must escape from immune cells, mainly from CTL, for the development of NPC.

In the EBV latent infection program, the most efficient strategy for immune escape is to keep the level of expression of the EBV antigen per cell as low as possible. Maintaining low antigen expression leads to low CTL epitope presentation in EBV-infected cells. Crotzer et al. reported that the presentation of PRIYDLIEL-like epitopes in EBNA3C is less than one epitope per cell [20], resulting in very low or no detection of EBV-transformed B-cells by CTL clones with high affinity to the peptide [21].

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In addition, EBV latent membrane protein 1 (LMP1) contains a Gly-Ara repeat domain that suppresses the translation of EBNA1 and prevents the processing of EBNA1, resulting in the inhibition of antigen presentation by MHC class I [22].

3. Superantigen Induction by EBV

One theory states that despite these mechanisms of immune evasion, some EBV gene expression leads to lymphocyte infiltration. This is one theory. The other theory is the induction of superantigens by EBV genes. Superantigens are microbial pathogen-derived proteins that induce strong T-cell responses. HERV-K18 was the first human endogenous provirus to originate from a retrovirus with superantigen activity [27]. HERV-K18 preferentially activates human TCRBV13 T cells [28]. Essentially, it exists in a dormant state. However, the expression of its *env* gene was observed in latently infected EBV cells. Sutkowski showed that both LMP1 and LMP2A are able to transactivate the HERV-K18 superantigen. Both LMP1 and LMP2A are expressed in NPC cells [29]. HERV-K18 may induce heavy T-cell infiltration, and the secretion of cytokines by the interaction of superantigen-expressing tumor cells with activated T-cells can contribute to the highly metastatic features of NPC [30][31].

4. Modulation of Immune Checkpoint in NPC

Generally, the number of intratumoral and stromal TILs is associated with a favorable prognosis in patients with NPC [19]. The programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axis plays an important role in T-cell tolerance and immune escape of tumor cells. PD-L1 expression is higher in EBV-positive than in EBV-negative NPC cell lines. It can be due to the abundant IFN-γ induction by EBV infection. In addition, LMP1 and IFN-γ

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pathways, cooperate to regulate PD-L1 [32]. LMP1 knockdown suppresses PD-L1 expression in EBV-positive cell lines. IFN-γ upregulates PD-L1 expression independently and synergistically with LMP1 in NPC tissue [33].

PD-1 is expressed on TIL, while PD-L1 is expressed in tumor and stromal cells. The interaction between PD-1 and PD-L1 suppresses CTL attacks on tumor cells [33]. Thus, the co-expression of PD-1 and PD-L1 in the tumor microenvironment usually predicts the recurrence and metastasis of NPC after initial therapy. Antibodies that block this pathway have been clinically used against various cancers, including NPC [18][34]. Adoptive T-cell therapy targeting the EBV gene products is a potential therapeutic strategy for NPC. PD-L1 expression in cancer cells can inhibit the effector functions of adoptively transferred EBV-specific T-cells. The combination of EBV-specific adoptive T-cell and PD-L1 blockade therapies has been reported to be more effective [35].

Several immunotherapies have been explored for NPC; however, these trials have yielded inconsistent conclusions, probably due to different immune microenvironments [33][34][36][37][38][39]. For example, LMP1 promotes myeloid-derived suppressor cell (MDSC) expansion in the tumor microenvironment by promoting extra-mitochondrial glycolysis in malignant cells. In addition to RAGE, LMP1 promotes the expression of multiple glycolytic genes, such as GLUT1. This metabolic reprogramming induces the NOD-like receptor family protein 3 inflammasome and activates the arachidonic cascade, which in turn activates various cytokines such as IL-1β, IL-6, and GM-CSF. These changes in the tumor environment result in NPC-derived MDSC induction [40].

5. Challenge for EBV Vaccine Development

The close association of EBV infection with NPC suggests that controlling EBV infection and targeting EBV-infected cells are effective strategies for preventing NPC development and managing developed NPC. However, despite the urgent need for prophylactic or therapeutic solutions, there has been no licensed EBV vaccine thus far [41]. The major obstacles to developing a prophylactic vaccine include the global prevalence of EBV and the fact that infection typically occurs during early childhood to adolescence, resulting in a limited number of control cohorts without EBV infection. In addition, the complexity of the EBV replication system and its infectivity to T lymphocytes and NK cells present challenges in eliminating all EBV target cells [41]. With recent advancements in messenger RNA vaccines, exemplified by their successful application in the COVID-19 pandemic, various viruses, including EBV, have been considered candidates for this technique [42]. Moderna has announced the initiation of a phase 1 study for its mRNA Epstein-Barr virus (EBV) vaccine, codenamed mRNA-1189. mRNA-1189 comprises five mRNAs encoding envelope glycoproteins (gp350, gH, gL, gp42, and gp220) that bind to target cell surface receptors, playing key roles in initiating EBV infection of target cells. The administration of mRNA-1189 aims to induce a broad immune response that could prevent EBV infection in various types of cells, ultimately reducing the symptoms of infectious mononucleosis. According to the manufacturer, preclinical testing of mRNA-1189 in mice and nonhuman primates demonstrated high and durable levels of antigen-specific antibodies against B cell and epithelial cell infection [43]. The announced phase 1 clinical trial (NCT05164094) will assess the safety and tolerability of three different doses of mRNA-1189 in healthy adults aged 18 to 30. The humoral immune response will be evaluated up to day 197 [44]. (https://clinicaltrials.gov/study/NCT05164094 (accessed on 11 October 2023)).

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