

# Effect of Epstein-Barr Virus Infection on the Treatment of Gastric Cancer in Tumor Immunotherapy

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**Abstract.** Gastric cancer is one of the biggest medical problems in the world today, and it is also a huge medical challenge for human beings. The main challenge is the complexity of the limitations of gastric cancer itself. At present, the efficacy of single-drug immune checkpoint inhibitors in treatment is not clear. It can be found in previous cases that Epstein-Barr virus positive gastric cancer patients have significantly higher response to PD-1 antibodies than the overall patients, from which it can be found that EBV infection can play an important role in gastric cancer immunotherapy. The purpose of this study was to investigate the effect of Epstein-Barr virus infection on gastric cancer and analyze specific clinical cases. The results showed that patients infected with Epstein-Barr virus had obvious advantages in the treatment of gastric cancer, which was significantly correlated with the expression of PD-L1 and EBV (+). This study highlights the potential benefits of Epstein-Barr virus infection in the treatment of gastric cancer, providing new insights into the development of future immunotherapy strategies. These findings will help to improve the treatment of gastric cancer patients, as well as to better understand the immune properties of gastric cancer and develop related vaccines. The significance of this study is that it provides a solid foundation for innovation in the treatment of gastric cancer.

**Keywords:** EBV; gastric cancer; immune checkpoint; Immune checkpoint inhibitor.

## 1. Introduction

Stomach cancer has become one of the second most common malignant tumors in our country, and the second reason of cancer-related death [1]. New immunotherapies are emerging all the time. With the deepening of cancer research, immunotherapy has become one of the most important research directions in the field of gastric cancer. PD-L1 plays a key role in immune escape mechanisms, and its high expression has been shown to be closely associated with poor prognosis in patients with gastric cancer. In this context, the introduction of immune checkpoint inhibitors provides a new prospect for the treatment of gastric cancer. (Epstein-Barrvirus) EBV is a gamma herpesvirus that causes tumors of multiple cell sources (such as B cells, T cells, NK cells, epithelial cells, and mesenchymal cells) [2,3]. EBVAGC (Epstein-Barr virus associated gastric cancer) is associated with EBV infection. EBV is mostly latent infection in human body. EBV carriers have a more than 18-fold higher risk of developing EBVAGC compared to those who do not carry EBV [4]. Studies in recent years have found that EBV infection is strongly associated with a variety of tumors [5]. However, the specific nature of EBVAGC makes immunotherapy potentially more complex in this subpopulation. Therefore, the goal of this study is to deeply explore the interaction between EBV and immunotherapy, so as to provide a more accurate and personalized program for gastric cancer immunotherapy. The complexity and heterogeneity of gastric cancer make immunotherapy face various challenges in its application. Gastric cancer escapes the killing of the immune system by down-regulating tumor expression, up-regulating immune checkpoint, inactivating cytotoxic T cells and changing tumor immune microenvironment. PD-L1 is a ligand of programmed cell death receptor 1 (PD-1), and the combination of the two can inhibit the activation of cytotoxic T cells and promote tumor cells to escape the monitoring and killing of the immune system [6]. Studies have reported that the up-regulated expression of PD-L1 can be detected in patients with gastric cancer and is closely related to tumor progression and patient prognosis [7]. EBVAGC consists of monoclonal tumor cells infected with EBV, accounting for 5% to 10% of gastric cancer [8]. The study of Derks et al. [9]



showed that about 15% of EBV (+) gastric cancer had genomic amplification in chromosome 9P22.1 region, which is the gene locus encoding PD-1 ligand (PD-1 and PD-2), so EBVAGC was more prone to high expression of PD-L1. Immune checkpoint inhibitors, including antiprogrammed cell death protein 1 (anti-PD-1) nanoantibodies (nivolumab, pembrolizumab), have opened up a new era in cancer therapy and changed the paradigm of cancer treatment. The purpose of this study was to investigate the relevance of Epstein-Barr virus in patients with gastric cancer, and how to use immunotherapy to intervene the mechanism of interaction between Epstein-Barr virus and tumor. This study will redefine tumors in a number of ways.

## **2. Immune Escape Mechanism of Tumor and Limitations of Immunotherapy**

The immune escape mechanism of tumor cells and the limitations of immunotherapy are important topics in the field of cancer therapy. Tumor cells can use a variety of ways to evade detection by the immune system, which makes immunotherapy a major challenge. First, tumor cells can reduce the expression of their antigens, which makes it difficult for the immune system to detect them. In addition, tumor cells are able to activate immunosuppressive pathways, such as PD-1/PD-L1, which inhibits immune cells from functioning, thus making them less aggressive against tumor cells. These strategies work together to make it extremely difficult for the immune system to recognize and clear tumor cells. Overcoming these mechanisms can improve the effectiveness of immunotherapy. Therefore, a deeper understanding of these mechanisms could lead to the development of better treatments in immunotherapy. In case-specific analysis, it can be found that not all patients show a significant response to immunotherapy, one of the important reasons may be that some patients lack sufficient active immune cells or have other inhibitors that reduce the effectiveness of immunotherapy. Therefore, specific treatment options need to be developed according to individual differences and the diversity of immune system states. Future studies need to further analyze the immune escape mechanism of tumor cells to find more precise intervention methods. At the same time, a deeper understanding of a patient's individual immune status is needed to better predict and optimize response to immunotherapy. Through the comprehensive application of multidisciplinary knowledge such as immunology, molecular biology and clinical medicine, it is expected to break through the limitations of current immunotherapy and bring effective treatment options to more cancer patients.

## **3. Application and Challenge of Immune Checkpoint**

Checkpoint inhibitors have made significant breakthroughs in the treatment of cancer; however, their application is not equally effective for every patient. A major challenge is that infiltration of immune cells within tumors is usually relatively limited, limiting the full use of drugs. Therefore, how to infiltrate more immune cells in tumor tissue is an urgent problem to be solved. Immune checkpoint inhibitors are drugs that "brake" the immune system to remove cancer cells, PD-1 and PD-L1 antibodies are the most common representatives, and their application plays a huge role in the treatment of cancer. These inhibitors help activate T cells to enhance the immune system's response to tumors by binding to PD-1 or PD-L1 molecules. However, immune checkpoint inhibitors do not have significant results in all patients. This may be related to the tumor microenvironment, one reason may be that gastric cancer patients have insufficient immune cell infiltration, enough immune cells to make them play a role, otherwise they cannot effectively activate existing immune cells T cells. In order to overcome this problem, a deeper understanding of the immune environment is needed to find ways to increase immune cell infiltration in gastric cancer patients. One possible option is to combine other treatments, such as chemotherapy or radiation, to stimulate more immune cells to come in. In addition, future research directions could develop better therapeutic strategies for the role of other immunosuppressive factors in the tumor microenvironment. Through various therapeutic means, it is expected to improve the therapeutic effect of immune checkpoint inhibitors on gastric cancer patients and open up new possibilities for personalized treatment.

#### 4. Effects of EBV on Gastric Cancer

The positive effects of EBV in gastric cancer have attracted people's attention. EBV infection can allow more infiltrating immune cells to enter the tissue, which can make gastric cancer better treated. In the case of EBV infection, tumors are more easily recognized and attacked by the immune system because these viruses can enable immune cells to reach gastric cancer cells. EBV is a widespread virus that has been linked to certain stomach cancer patients. In some cases, EBV infection may have a specific role in the development of stomach cancer. One possible mechanism is to alter the immune environment of the tumor by promoting tumor invasion and the entry of immune cells into tumor tissue. Specifically, more T cells and B cells infiltrate the tumor tissue through EBV infection, and more of these cells are better for treating gastric cancer. The occurrence of this phenomenon suggests that the immune system's response to gastric cancer enhances infection through EBV, thereby enhancing the potential effectiveness of the immune checkpoint inhibitors. This is of great significance to further understand the interaction mechanism between EBV and immunotherapy, and to provide more personalized and precise treatment for gastric cancer patients. Future studies are needed to dig deeper into these mechanisms to better leverage the presence of EBV to optimize treatment strategies for patients with gastric cancer.

#### 5. Analysis of Clinical Cases

It has been observed that the immune effect of people infected with EBV may be better than that of uninfected people because immune cells are more likely to infiltrate tumors. This provides support for EBV infection as a potential treatment strategy.

In a study exploring the relationship between PD-L1 expression and EBV (+), the researchers analyzed 227 gastric cancer tissue samples and found that the incidence of EBV (+) was 7.05%. As shown in Table 1, EBV (+) gastric cancer showed a higher PD-L1 positive rate, while EBV (-) gastric cancer had a PD-L1 positive rate of 38.39%. Studies have shown that the expression of PD-L1 in gastric cancer tissues is significantly correlated with EBV (+) [10]. This provides important clues for understanding the immune characteristics of EBV-associated gastric cancer, and has guiding significance for future research and treatment strategies.

**Table 1.** Positive rate of PD-L1 in EBV (+) gastric cancer samples [10]

	EBV (+) Gastric cancer	EBV (-) Gastric cancer
Number of PD-L1 positives	11	81
Positive rate of PD-L1	68.75%	38.39%

In addition to the amplification of 9p24.1, EBV (+) gastric cancer also has abundant IFN- $\gamma$  immune response characteristics, and IFN- $\gamma$  released by tumor infiltrating T cells (TIICs) can directly induce tumor and immune cells to express PD-L1. EBV (+) gastric cancer may also have other mechanisms to induce PD-L1 expression, such as classical Hodgkin lymphoma with EBV (+), which also increases the expression level of PD-L1 due to the EBV-induced AP-1 expression and the activation of JAK/STAT signal [11]. These studies suggest that EBV (+) gastric cancer has multiple mechanisms to induce PD-L1 expression and suggest that PD-1-driven immune escape may play an important role in EBV (+) gastric cancer.

#### 6. Future Personalized Treatment of Gastric Cancer With EBV

Currently, personalized vaccines are showing some encouraging success in the field of cancer treatment. For example, there has been some progress in developing a personalized vaccine for malignant melanoma. Since the beginning of the 21st century, a large number of tumor vaccine clinical trials have been conducted worldwide, and there are currently 348 melanoma vaccine studies registered on the US Clinical Trial Database website. However, the relevant research is not mature, the lack of multi-center large sample clinical trials, the effectiveness is uneven, the current tumor

vaccine can only be used as an adjuvant treatment, there is no domestic approved market white melanoma vaccine. It is undeniable that with the concept of neoantigens, tumor vaccine as a new method of immunotherapy has attracted wide attention. It is believed that personalized tumor vaccine will become an important measure for melanoma treatment and clinical transformation in the near future [12]. Researchers use a patient's own tumor tissue to extract antigens and prepare personalized vaccines that fight tumors by stimulating the immune system. Preliminary results from this approach suggest that in some cases, personalized vaccines are able to induce an immune response and have a positive effect against cancer cells. With the deepening understanding of the role of EBV in gastric cancer immunotherapy, personalized treatment strategies have become increasingly compelling. One possible approach is to use EBV infection to boost the immune system's response to stomach cancer, especially in those patients with insufficient infiltration of immune cells. One potential strategy is to develop EBV as a vaccine carrier to boost the immune system's response to tumors. This suggests that EBV can be prepared as a vector through which immune cells can better enter tumor cells.

T cells and B cells will be better activated and increase invasion in the tumor, which will help immunotherapy.

## **7. Conclusion**

The study suggests that the function of the immune system is affected by EBV. EBV infection is related to the activity and distribution of immune cells in the tumor, which can be seen why EBV-positive gastric cancer patients are affected.

Treatment with PD-1 antibodies is more effective. In addition, EBV infection may affect targeting immunotherapy by altering molecules on the surface of tumor cells. Although EBV plays a positive role in immunotherapy, more in-depth research is needed to elucidate the mechanisms by which EBV infection can affect immunotherapy and provide clues for further improvement.

Treatment response in patients with gastric cancer. Future research in this area is expected to provide new directions for the development of more effective immunotherapy strategies. Gastric cancer is one of the second most common malignant tumors in our country, and immunotherapy provides a new way to treat it. However, the immune escape mechanism of gastric cancer patients, especially the insufficient infiltration of immune cells, has become the main constraint of current immunotherapy. In this context, in-depth research and innovative treatment strategies are urgently needed to improve the effectiveness of immunotherapy. The introduction of immune checkpoint inhibitors has brought new therapeutic opportunities for gastric cancer patients. Inhibitors of the PD-1/PD-L1 pathway have shown potential efficacy in clinical applications, but not all patients will benefit from them. Individual differences and limitations of immunotherapy are urgent problems to be solved. Tumor cells evade the attack of the immune system through various mechanisms, such as reducing the expression of antigens and activating immunosuppressive pathways, which limit the effect of immunotherapy. In addition, there is insufficient infiltration of immune cells in the tumor microenvironment, making some patients respond less than desirable to immune checkpoint inhibitors. To overcome these challenges, future studies will closely combine multidisciplinary knowledge to dig deeper into the immune characteristics of individuals with gastric cancer. The formulation of individual treatment strategy and the combined use of multiple treatment methods may be the key to improve the therapeutic effect. Through in-depth understanding of the infiltration of immune cells in tumor tissues, promoting the entry of immune cells may be an effective way to improve the effect of immunotherapy. With the continuous progress of medical science and technology, vaccine research for EBV-related diseases is trying to explore new directions. First, a deeper understanding of the biology of EBV will provide critical information for vaccine design, ensuring broad coverage of EBV variants. Second, through innovative vaccine technology, it is hoped that more dynamic EBV vaccines can be designed to stimulate a more adequate response from the immune system. Clinical trials will further validate the safety and efficacy of the vaccine and ensure its practical application in preventing EBV infection and related diseases. Future EBV vaccine

research will also strengthen integration with advanced biotechnology and bioinformatics. Through personalized vaccine design, considering the immune status and genetic differences of patients, the success rate of vaccination can be improved. Continuous innovation in this area will provide more sustainable solutions for the prevention and control of EBV-associated diseases. Therefore, the future development of immunotherapy and vaccine research will open up a broader prospect for the treatment and prevention of gastric cancer and related diseases.

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