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Review

The immune microenvironment in Epstein–Barr virus-positive gastric cancer: current status and future perspectives

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Abstract: We have previously discussed the pathological characteristics, clinical characteristics, detection methods, pathogenesis, and treatment of Epstein–Barr virus (EBV)-positive gastric cancer, but we have not discussed the unique immune microenvironment in EBV-positive gastric cancer. Here, we reviewed studies on the immune microenvironment in EBV-positive gastric cancer and found that CD8+ T lymphocytes and a small number of CD204+ macrophages infiltrate the immune microenvironment in EBV-positive gastric cancer. Moreover, immune checkpoints, such as IDO1 and PD-L1, are expressed at high levels in EBV-positive gastric cancer. Lastly, we also analyzed the mechanisms underlying the formation of the immune microenvironment in EBV-positive gastric cancer. Our findings and conclusions have significance in clinical guidance and provide research direction for basic experiments.

Keywords: Epstein–Barr virus; gastric cancer; immune microenvironment.

1. Introduction

Gastric cancer is the most common malignant tumor [1]. Most patients with gastric cancer have advanced gastric cancer during diagnosis [2]. In addition, gastric cancer is not only highly malignant but also highly heterogeneous, which increases the challenges in its treatment. The Cancer Genome Atlas (TCGA) has reported the comprehensive identification of genetic changes associated with gastric cancer and further divided this form of cancer into four subtypes: Epstein–Barr virus (EBV)-positive tumors (9%), microsatellite unstable (MSI) tumors (22%), genetically stable tumors (20%), and chromosome-unstable tumors (50%). Moreover, EBV-positive and MSI gastric cancers can respond to immunotherapeutic drugs [3]. In previous studies, we reviewed findings on EBV-positive gastric cancer [4]. Based on the characteristics of EBV-positive gastric cancer, the methods for testing EBV-positive gastric cancer, the mechanism underlying the occurrence and development of EBV-positive gastric cancer, and the relationship between EBV-positive gastric cancer and responses to immunotherapy were explored. The detection method, pathogenesis, and treatment of also EBV-positive gastric cancer were explored. However, with the increasing number of studies on EBV-positive gastric cancer, our understanding of it is also improving. One of the most important concerns is the composition of the immune

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microenvironment in EBV-positive gastric cancer. In this review, we discuss the immune microenvironment in EBV-positive gastric cancer to provide guidance for clinical practice and research ideas for basic experiments.

2. Immune cell infiltration in EBV-positive gastric cancer

After EBV invades the host, it causes a series of immune responses in the host [5]. This suggests that the composition of the immune microenvironment in EBV-positive gastric cancer is destined to be different from that in other gastric cancers[6]. The gene expression profiling of patients with EBV-positive gastric cancer shows significant changes in immune response genes that may enable the recruitment of reactive immune cells and improve patient survival outcomes in EBV-positive gastric cancer [7]. EBV-positive gastric cancer is characterized by high and low densities of CD8+ T cells and CD204+ macrophages, respectively [8,9]. Infiltrating immune cells and the specific immune microenvironment contribute to antitumor immunity [10].

After EBV invades the host, it first induces a non-specific immune response dominated by the production of macrophages. Several studies have also shown that macrophage infiltration in EBV-associated gastric cancer is different from that in other gastric cancers. A 2016 study by Takashi et al. [9] showed that the infiltration of CD204-positive M2 macrophages was lower in EBV-associated gastric cancer. In 2020, Song et al. [11] showed that EBV-encoded miR-BART11 promotes the metastasis of gastric cancer by targeting FOXP1 in gastric cancer to promote tumor-associated macrophage-induced epithelial-mesenchymal transition. EBV infection will eventually initiate cellular immunity, which represents the activation of CD8+ T cells, and the most important anti-tumor cells in the human body are CD8+ T cells [12]. As early as 1996, Saiki et al.[13] showed that a large number of CD8+ T cells infiltrate the tumor microenvironment in EBVaGC. In 2018, de Rosa et al.[14] reported a high degree of CD8+ T cell infiltration in EBVaGC. In the same year, Tang et al.[15] showed that the expression of CCL21 in EBV-related gastric cancer cells protected CD8+CCR7+ T lymphocytes from apoptosis through a mitochondria-mediated pathway. Moreover, multiple studies have shown that the infiltration of CD8+ T cells is positively correlated with the survival of patients with gastric cancer [16,17]. However, not all EBVaGCs have a good prognosis. In 2015, Zhang et al.[18] showed that even though EBVaGCs were accompanied by extensive CD8+ T lymphocyte infiltration, some patients did not show a good prognosis, because CCL22 produced by EBVaGC cells enhanced the recruitment of CD4+CD25+FOXP3+ Tregs, and these Tregs had higher proliferation rates and lower apoptosis rates at the tumor sites.

3. Expression of immune checkpoint proteins in EBV-positive gastric cancer

Tumor cells in EBVaGC evade immune responses through multiple strategies. Reportedly, indoleamine-pyrrole 2,3-dioxygenase (IDO1) is a potent immunosuppressive enzyme, and IDO1 suppresses the host antitumor immune responses by depleting tryptophan in the tumor microenvironment, thus inhibiting T cells from mounting immune responses against tumors [19]. Many studies have shown that IDO1 is upregulated in EBVaGC [20].

EBVaGC cells were also found to be characterized by the expression of high levels of programmed death ligand 1 (PD-L1) and the extensive infiltration of immune cells in the microenvironment[21]. Since tumor cells recruit PD-L1 to interact with programmed cell death protein 1 (PD-1) on the surface of T cells to evade anti-tumor immunity, high PD-L1 expression in EBVaGC is considered to be associated with tumor progression [22]. In addition, some studies have also shown that PD-L1 expression is increased in patients with EBV-positive gastric cancer, whereas patients with MSI gastric cancer have a better prognosis [23,24]. To explore the underlying mechanism, in 2020, Chen et al.[25] used in vitro transfection to confirm that EBV-encoded miR-BART5-5p upregulates PD-L1 through PIAS3/pSTAT3 regulation, thereby enabling gastric cancer cells to escape immune surveillance.

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4. Immunotherapy in EBV-positive gastric cancer

Evidence from previous studies has shown that tumors caused by microorganisms have good therapeutic effects, which may be related to the greater immunogenicity of proteins expressed by microorganisms. Kim ST introduced immunotherapy in the treatment of EBV-positive gastric cancer. In the study, published in 2018[26], he conducted molecular characterization of tissue and circulating tumor DNA (CtDNA) in 61 patients with metastatic gastric cancer who received pembrolizumab salvage therapy in a prospective phase 2 clinical trial. The objective response rate (ORR) of pembrolizumab in the treatment of EBV-positive metastatic gastric cancer was 100%, which was significantly higher than the ORR of 85.7% in the treatment of MSI metastatic gastric cancer. This indicated a high correlation between PD-L1 positivity and EBV positivity/MSI-H, suggesting that EBV-positive gastric cancer may represent another disease with higher potential for clinical benefits from immunotherapy compared to that in patients with MSI-H. In 2020, the research team once again validated the effectiveness of immunotherapy in the treatment of EBV-positive gastric cancer[27]. Three hundred Asian patients with gastric cancer were included in this study, of which 178 patients (59.3%) tested positive for PD-L1Cps≥1, and 122 patients (40.7%) tested positive for PD-L1Cps<1. PD-L1Cps ≥1 was associated with stage I tumors (P=0.022), high microsatellite instability (MSI-H) (P<0.001), EBV positivity (P=0.008), and Helicobacter pylori status (P=0.001). With respect to the gene expression profiles, PD-L1CP expression showed a high correlation with the mutational burden (P < 0.001), EBV subtype (P < 0.001), and microsatellite virus subtype (P < 0.001). PD-L1 was expressed in 59.3% of patients with gastric cancer and was associated with the positive expression of MSI and EBV. These results suggest that patients with EBV-positive gastric cancer may benefit from immunotherapy.

5. Mechanism underlying immune microenvironment development in EBV-positive gastric cancer

Gastric cancer caused by EBV primarily occurs through three pathways: latency protein, miRNA, and DNA methylation, among which the most important oncogenic pathway is the latency protein pathway. The major latency proteins are EBER, EBNA-1, BARF-0, BARF-1, and LMP2A [28–31], and the pathways activated by these proteins can promote not only tumorigenesis but also the migration of immune cells and the formation of an immune microenvironment. Among these proteins, EBER is related to the IL-6-STAT3 signaling pathway [30]. BARF-0 and BARF-1 can induce changes in the NF-κB/miR-146a/Smad4 pathway [32–34]. LMP2A can activate the NF-κB-survivin pathway [35,36], mediate Notch signaling, and promote mitochondrial division and cell migration [37]. LMP2A downregulates TET2, COX-2, and HLA [38–40] and upregulates FOXO1 and FOXO3 [41]. LMP2A activates the PI3K/AKT pathway to mediate transformation and inhibit transforming growth factor β1-induced apoptosis [42]. LMP2A induces STAT3 phosphorylation, leading to DNMT1 transcriptional activation and PTEN promoter methylation [43]/ LMP2A activates CpG island methylation at the AQP3 promoter and induces ERK phosphorylation [44]. The activation of these pathways is closely related to the formation of the immune microenvironment.

Another major function of EBV is that it promotes the development of gastric cancer via miRNA. The EBV genome can encode more than 40 miRNAs, such as ebv-miR-BART-1-3p, -2-5p, -3-3p, -4-5p, -5- 5p, -7-3p, -9-3p, -10-3p, -17-5p, -10-3p, -18-5p, BART11, among others [45–50]. These miRNAs affect immune responses and antigen presentation and recognition, alter communication between T and B cells, drive antibody production during infection, and play a role in apoptosis. Among them, the EBV miRNA BART11 can downregulate the Foxp1 transcription factor, affect the tumor microenvironment, promote epithelial-mesenchymal transition, and accelerate tumor invasion and metastasis [11]. BART3-3p can inhibit senescence in nude mouse gastric cancer cells by altering the

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senescence-associated secretory phenotype (SASP) and can inhibit the infiltration of natural killer cells and macrophages into the tumor [51]. miR-BART16 abrogates the expression of IFN-stimulated genes in response to IFN-α stimulation and suppresses the antiproliferative effect of IFN-α in latently infected cells [52]. The regulation of LMP2A expression by newly discovered EBV-encoded microRNAs, miR-BART22[53] and miR-BART17-5p, promotes migration and anchorage-independent growth by targeting kruppel-like factor 2 in gastric cancer[54,55]. miR-BART15-3p target anti-apoptotic TAX1BP1 and NLRP3 genes in cancer cells, thereby increasing apoptosis [3,56,57]. These miRNAs are closely related to the development of the immune microenvironment.

6. Summary and prospects

Here, we reviewed publications related to the immune microenvironment of EBV-positive gastric cancer, starting with the infiltration of immune cells to the expression of immune checkpoints in EBV-positive gastric cancer and eventually the mechanism underlying the formation of the immune microenvironment in EBV-positive gastric cancer. This review provides a complete overview of the immune microenvironment in EBV-positive gastric cancer. The findings allow us to better understand the immune microenvironment in EBV-positive gastric cancer and identify better treatment plans. However, our understanding of EBV-positive gastric cancer is still preliminary, and some challenges and treatment options remain unexplored and are yet to be discovered. Therefore, we believe that further research and a better understanding of EBV will play a crucial role in the treatment and prognosis of patients with gastric cancer.

Figures

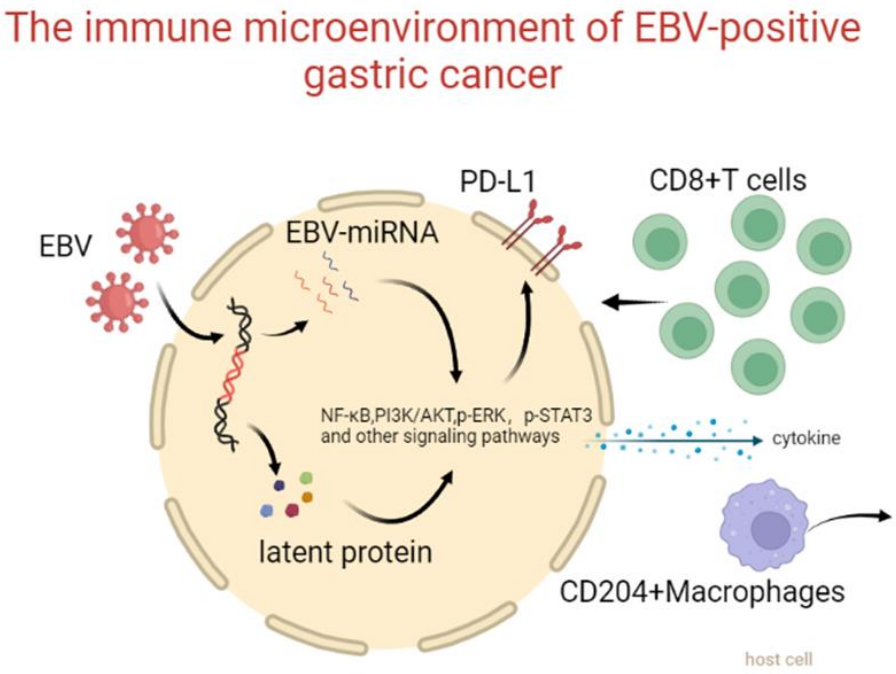

Figure 1. Summary diagram.

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