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Research Progress on Anti-PD-1 and PD-L1 Immunotherapy for Gastric Cancer

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Abstract: ***Gastric cancer (GC) is a globally prevalent disease that poses a significant threat to human health and quality of life. With advancing research on tumor immune evasion mechanisms, programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) have been demonstrated to interact with the tumor microenvironment and mediate tumor immune evasion. This article reviews the latest research progress in this field, explores their expression in gastric cancer, and discusses the therapeutic effects and prospects of targeted drugs, aiming to provide insights for personalized and precision medicine strategies. These efforts seek to reduce patient recurrence and metastasis risks while improving clinical outcomes.***

Keywords: Gastric cancer, Immunotherapy, PD-1/PD-L1.

1. Introduction

Gastric cancer is the fifth most common cancer globally and the third leading cause of cancer-related deaths. In 2022, it ranked fifth in both new cases and deaths worldwide (969,000 cases and 660,000 deaths, respectively). In China, the standardized incidence rate of gastric cancer ranked 15th globally (40.8 per 100,000) and the standardized mortality rate ranked 24th (26.7 per 100,000). This indicates that gastric cancer remains a significant threat to human health worldwide [1]. Its risk factors include Helicobacter pylori infection, age, high salt intake, and diets low in fruits and vegetables. Gastric cancer is diagnosed histologically after endoscopic biopsy and staged using CT, endoscopic ultrasound, PET, and laparoscopy. It is a highly heterogeneous disease at both molecular and phenotypic levels [2]. As a common malignant tumor with poor prognosis, surgical treatment remains the first-line curative approach. Although the 5-year survival rate for early-stage gastric cancer can exceed 90%, and prospective studies have confirmed the safety and feasibility of laparoscopic surgery for early-stage gastric cancer, most patients are diagnosed at advanced stages due to low early detection rates. Therefore, treatment modalities for advanced gastric cancer require further exploration and validation [3]. Currently, cytotoxic chemotherapy remains the cornerstone of treatment for metastatic gastric cancer worldwide. However, recent advances in understanding gastric cancer molecular mechanisms have brought hope for therapeutic strategies, such as targeted drugs to improve survival rates and reduce toxicity. Immunotherapy is now recognized as an innovative approach for treating cancers including lung cancer, gastric cancer, and breast cancer. A large number of clinical trials have also demonstrated the promising future prospects of targeted therapy for gastric cancer [4,5]. Despite the high incidence of gastric cancer (GC), unfortunately, most patients are diagnosed at advanced stages with poor prognosis due to the lack of clear clinical indications [6,7]. Systemic chemotherapy remains the primary treatment for metastatic gastric cancer (mGC); therefore, cutting-edge diagnostic technologies and immunotherapeutic agents are crucial for improving treatment outcomes. Emerging advancements in immunotherapy, particularly anti-HER2 therapies, along with biomarker-targeted therapies for GC, have recently disrupted this trend. For instance, anti-programmed cell death 1 (PD-1) antibodies have shown remarkable efficacy and prolonged survival in untreated MSI-H/dMMR mGC patients [8].

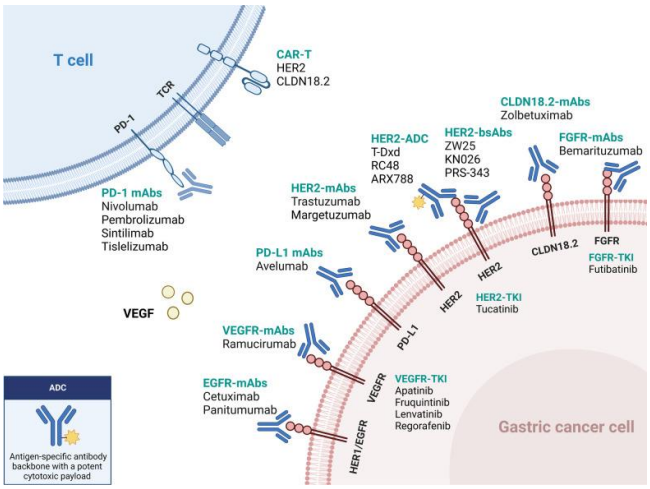

Figure 1: Immunotherapy and targeted therapy for gastric cancer

The Figure 1 illustrates immunotherapy and targeted therapy for gastric cancer. This algorithm provides guidance for selecting currently available immunotherapies and targeted therapies based on different biomarkers [9]. (Figure 1)

2. Pathogenic Mechanisms of PD-1 and PD-L1

Programmed cell death protein 1 (PD-1), also known as CD279, was first discovered in 1992. It is a 50-55 kDa type I transmembrane glycoprotein containing 288 amino acids, with an extracellular N-terminal domain, a transmembrane domain, and a cytoplasmic tail located at the N-terminus and C-terminus, respectively, which contains two tyrosine residues. PD-1 serves as an inhibitor of adaptive and innate immune responses and is expressed on activated T cells, natural killer (NK) cells, B lymphocytes, macrophages, dendritic cells (DCs), and monocytes. Notably, PD-1 is highly expressed on tumor-specific T cells. PD-1 plays a critical role in modulating ineffective or harmful immune responses and maintaining immune tolerance [10]. Programmed cell death ligand 1 (PD-L1), also referred to as CD279 or B7-H1, belongs to the B7 family and is a 33 kDa type I transmembrane glycoprotein containing 290 amino acids,

with an extracellular region comprising Ig-like and IgC domains. PD-L1 is typically expressed by macrophages, certain activated T cells and B cells, DCs, and some epithelial cells. Additionally, PD-L1 is expressed by tumor cells as an "adaptive immune mechanism" to evade antitumor responses. PD-L1 has been demonstrated to exert non-immunomodulatory proliferative effects on various tumor cell types [11]. According to the ToGA study, the addition of trastuzumab to chemotherapy can improve overall survival (OS) in patients with metastatic HER2-positive gastric cancer (GC) [12]. Furthermore, studies have demonstrated certain perioperative efficacy in this treatment regimen, although the associated survival benefits remain unsupported by definitive clinical data [13]. PD-1 is a checkpoint protein that binds to its ligands PD-L1 and PD-L2, thereby inducing natural killer (NK) cell-mediated cytotoxicity against T cells and B cells. In normal organisms, PD-1 acts as a negative regulator of T cell and B cell proliferation, playing a critical role in maintaining immune tolerance. In patients with tumors or viral infections, upregulated PD-L1 and PD-L2 bind to PD-1 receptors on T cell surfaces, suppressing T cell activity and impairing their function [14-17]. Two primary mechanisms involve PD-1/PD-L1 in tumor immune evasion: one is aberrant activation of the tumor-intrinsic Stat3-PI3K-Akt signaling pathway, leading to PD-L1 overexpression [10]; the other is interferon-β acting as a key driver of PD-1 expression and promoting PD-L1 expression in tumors [18].

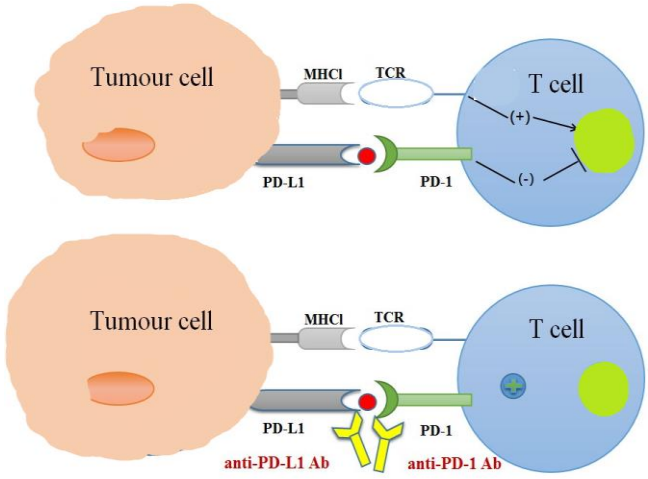

Figure 2: Tumor cells evade antigen-specific T cell immune responses by binding PD-L1 to PD-1 receptors

The figure 2 above illustrates how tumor cells evade antigen-specific T-cell immune responses by binding PD-L1 to PD-1 receptors. Blocking antibodies targeting PD-1 or PD-L1 can inhibit this mechanism, thereby enhancing antitumor immune activity against tumor cells. TCR: T-cell receptor; MHC1: Major Histocompatibility Complex I; Ab: Antibody.

The PD-1 pathway has garnered widespread attention due to its role in triggering T-cell immune checkpoint responses, enabling tumor cells to evade immune surveillance and exhibit high resistance to conventional chemotherapy. The application of anti-PD-1/PD-L1 antibodies as checkpoint inhibitors is rapidly emerging as a promising cancer treatment modality, with several antibodies having been successfully commercialized in recent years [19].

3. Current Status of Gastric Cancer Treatment

Current treatment modalities for gastric cancer include surgical intervention, cytotoxic therapy, targeted therapy, cellular structural remodeling therapy, targeting of DNA damage repair proteins, and immunotherapy. For patients with early-stage gastric cancer (stage II or below), tumor resection is preferred over systemic chemotherapy. The surgical approach for stage II or below gastric cancer depends on tumor location and depth of invasion, but typically involves endoscopic mucosal resection, distal esophagectomy, subtotal gastrectomy, or total gastrectomy [20]. Advanced gastric cancer patients still primarily undergo surgical treatment, combined with peritoneal chemotherapy and hyperthermic perfusion to improve postoperative outcomes. With the advent of personalized and individualized medicine, treatment strategies for advanced gastric cancer continue to evolve [2].

4. Anti-PD-1 and PD-L1 Immunotherapy

Studies have demonstrated that anti-PD-1/PD-L1 immunotherapy can confer benefits in long-term survival with fewer adverse effects. It enhances the body's innate immune response by promoting targeted action and destruction of cancer cells. Current research indicates that for the treatment of advanced gastroesophageal cancer, anti-PD-1/PD-L1 immunotherapy exhibits superior therapeutic efficacy compared to chemotherapy or palliative care, with significantly higher long-term survival rates and lower incidence of adverse effects [21]. PD-1 inhibitors, as clinically commonly used immune checkpoint inhibitors, can alleviate immune suppression, activate anti-tumor immune responses, and improve antitumor outcomes. They demonstrate favorable antitumor efficacy in patients with unresectable advanced tumors, showing promising clinical prospects [22]. Global studies currently suggest that combining chemotherapy with PD-1 inhibitors can prolong survival and enhance antitumor outcomes in patients with advanced tumors [23].

5. Summary and Outlook

Gastric cancer, as one of the most highly hazardous malignant tumors worldwide, has seen continuous scientific research on its pathogenesis and progression, with therapeutic exploration remaining an ongoing advancement. Beyond conventional surgical interventions and pharmacotherapy, immunotherapy has demonstrated significant efficacy in recent years, particularly PD-1/PD-L1-targeted therapy, which stands as the optimal choice among immunotherapeutic modalities for gastric cancer patients, yielding substantial improvements in survival rates and prognosis. However, limited treatment options remain available for patients with low PD-1/PD-L1 expression levels or those exhibiting immune resistance. Consequently, multi-target immunotherapy and combination immunotherapy represent future therapeutic directions, while precision and personalized medicine signify emerging trends in oncology treatment. Critical challenges include translating the short-term efficacy of immunotherapy into long-term patient survival outcomes, as well as evaluating individual immune tolerance responses and treatment benefits to maximize therapeutic outcomes—a field requiring further investigation and assessment.

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