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Review Article

The significance and therapeutic potential of PD-1 and its ligands in ovarian cancer: A systematic review

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HIGHLIGHTS

- Ovarian cancer is one of the most common malignant tumors in women.
- The emerging immunotherapy represents a rational approach for cancer treatment.
- Immunotherapy may play a significant role in clinical management of ovarian cancer.

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ABSTRACT

Surgery, radiotherapy and chemotherapy are the mainstay of malignant cancer treatments. However, with the development of immunology, the emerging immunotherapy represents a rational and alternative approach for the treatment of human cancer, including ovarian cancer (OC). Based on a body of evidence and the clinical success of immunotherapy in many malignancies, it is confirmed that blocking the programmed death 1 (PD-1) and its ligands in OC is feasible and valid both in animal models and patients. Immunotherapy may play a significant role in the future clinical management and improve the prognosis of OC. This review will focus on the biological functions, treatment response, toxicity and viable target of PD-1 and its ligands in OC. Recognition of the multiple functions of PD-1 and its ligands in ovarian cancer will serve to deepen our understanding of the nature of OC, develop novel immunotherapy approaches and discover possible diagnostic and prognostic biomarkers in future clinical decisions.

Contents

Abbreviations: aa, amino acid; Bcl-2, B-cell leukemia 2; CTLA-4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; EMA, Europe Medicine Agency; FDA, Food and Drug Administration; GITR, glucocorticoid-induced TNFR related protein; Ig, immunoglobulin; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; mAb, monoclonal antibodies; NK, natural killer; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, overall response rate; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TIL, tumor-infiltrating lymphocyte.

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1. Introduction

Ovarian cancer (OC) is one of the most common malignant tumors in women. In 2012, there were an estimated 238,700 new cases of ovarian cancer worldwide leading to over 150,000 deaths [1]. Owing to the limited screening tools and nonspecific symptoms, most patients are diagnosed at an advanced stage. The 5-year survival rate with early pelvic disease is over 70% but less than 30% for those with advanced stage [2]. The majority of patients who initially achieve remission following the end of treatment eventually relapse within 16–18 months and die from the disease despite response to first-line therapy consisting of debulking surgery and chemotherapy [3,4]. Therefore, innovative and effective therapeutic practice need to be integrated into OC treatment strategies to achieve durable clinical prognosis. The immune system is able to recognize and eradicate cancer cells via multiple and complex mechanisms. Immunotherapies of blocking antibodies have showed great potential and the clinical effects were remarkable [5]. In this review, we present an overview of the biological understanding, current progress and future prospect of PD-1 and its ligands in OC.

1.1. Expression and biological functions of PD-1 and its ligands

The role of immunotherapy in cancer treatment has been identified decades ago. Currently, cancer immunotherapies include therapeutic vaccines, adoptive T-cell transfer, cytokines, immune modulators and immune checkpoint inhibitors [6]. Evidence accumulated over the past several years convincingly shows that OCs are immunogenic tumors. Monoclonal antibodies (mAb) that block PD-1 signaling pathway hold great potential as a novel cancer immunotherapy including melanoma, renal cell cancer, non-small cell lung cancer (NSCLC) and ovarian cancer [7].

1.1.1. Expression and biological functions of PD-1

The PD-1 gene (also known as CD279), a novel member of the immunoglobulin gene superfamily, was discovered in 1992 as a gene upregulated in a T cell hybridoma and hematopoietic progenitor cell line. The activation of the PD-1 gene involves in the classical type of programmed cell death [8]. PD-1 is a 288 amino acid (aa) type I transmembrane protein and composed of an immunoglobulin (Ig) superfamily domain, a ~ 20 aa stalk, a transmembrane domain, and an intracellular domain of approximately 95 residues containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) as well as an immunoreceptor tyrosine-based switch motif (ITSM). PD-1 is encoded by the Pdcd1 gene on chromosome 1 in mouse and chromosome 2 in human and is expressed on T cells, B cells, natural killer T (NKT) cells, activated monocytes, and dendritic cells (DCs) [9]. PD-1 has PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273) two biological ligands [10]. PD-1-PD-L1/PD-L2 ligation results in the phosphorylation of intracellular tyrosines in ITIM and ITSM which bind SHP-1 and SHP-2 to deliver an immunosuppressive signal into the T cell by down regulating T cell differentiation and regulating Bcl-XL expression [11].

1.1.2. Expression and biological functions of PD-L1

PD-L1 (B7-H1, CD274) is a 290 aa type I transmembrane protein encoded by the Cd274 gene on mouse chromosome 19 and human chromosome 9. PD-L1 consists of an IgV-like domain, IgC-like domain, signal sequence, transmembrane domain and intracellular domains [9]. PD-L1 is often expressed by activated cells including T cells, B cells, DCs, NK cells, monocytes/macrophages, activated vascular endothelial cells, mesenchymal stem cells and cultured bone marrow-derived mast cells [10]. PD-L1 is also found to be expressed in human carcinomas of lung, ovary, colon and melanomas [12]. Cancer cells generate lots of abnormal genes and proteins, which can be used as antigen to activate T cells. The activated effector T cells can secrete interferon-γ (IFN-γ) when antigen-specific immunity develops [13]. IFN-γ is expected to work as an antitumor agent, nevertheless, IFN-γ also upregulates PD-L1 expression on tumor cells to promote tumor progression [14]. The anti-PD-1 antibodies play a significant role in immunotherapy by blocking the combination of PD-1 on T cells and PD-L1 on tumor cells.

1.1.3. Expression and biological functions of PD-L2

PD-L2 (B7-DC, CD273), like PD-L1, is also a type I transmembrane comprised of a signal sequence, IgV-like domain, IgC-like domain, stalk, transmembrane domain and cytoplasmic domains. In contrast to PD-L1, the expression of PD-L2 is restricted to macrophages and DCs [11]. NF-κB、GM-CSF、IL-4、IFN-γ can induce the expression of PD-L2 [9]. Now researchers regard PD-L1 as the main ligand of PD-1, while study has found that the interaction of PD-1/PD-L2 exhibited a 2–6-fold higher affinity compared with the interaction of PD-1/PD-L1. PD-L2 is competitive with PD-L1 when combined with PD-1 [15].

1.2. PD-1/PD-L1 inhibitors in the ovarian cancer immunotherapy

1.2.1. Rationale for targeting PD-1 and its ligands in ovarian cancer

There is evidence of an immune response against OC in patients. A crucial step in establishing the validity of OC immunotherapy was the observation that $CD3^+$ tumor-infiltrating T cells correlated with improved overall survival [16]. Later research confirmed the significance of tumor-infiltrating lymphocytes (TILs) and specifically identified the $CD3^+$, $CD8^+$ T cells as important antitumor effectors [17]. These data highlight the major role of immune response in OC. To kill cancer cells effectively, anticancer immune system initiates a series of stepwise events, which called Cancer-Immunity Cycle. Neoantigens created by oncogenesis are released and captured by DCs for processing. Then DCs present the captured antigens on MHCI and MHCII molecules to T cells and the effector T cell responses against the cancer-specific antigens. Finally, the activated effector T cells traffic to and infiltrate the tumor bed to kill their target cancer cells through TCR and MHCI interaction [18]. However, tumors employ multiple strategies to attenuate the effectiveness of T-cell-mediated attack in turn by deregulation of antigen-presenting cells, establishment of a physical barrier at the vasculature, suppression of effector lymphocytes and activation of immunosuppressive cells [19]. Therefore, immunotherapies aimed at increasing the host immune response or decreasing immunosuppression are the key to OC.

1.2.2. Strategies for targeting PD-1 and its ligands in ovarian cancer

The PD-1 and its ligand PD-L1 represent a promising immune checkpoint pathway that can be blocked to reverse tumor-mediated immunosuppression. Studies confirmed the therapeutic potential of targeting this immune checkpoint pathway and anti-PD-1/PD-L1 antibodies have been evaluated in clinical trials as Table 1 shows. PD-1/PD-L1 pathway antibodies demonstrated an unprecedented durable response in patients with advanced melanoma, which led to a first FDA