REVIEW ARTICLE

Role of Immune Inhibitors in Ovarian Cancer

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ABSTRACT

Immune checkpoints have come to the front of cancer therapies as a powerful and auspicious strategy. Evidences have suggested that immunotherapy for ovarian cancer is effective. However, the functions of some immune checkpoints such as lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin and mucin-domain containing-3, B7-H3, and B7-H4 in ovarian cancer remain largely unexplored. This review encompasses the key that has been found to play a role in ovarian cancer. The review will provide an overview of the existing preclinical data and antitumor efficacy for each checkpoint with respect to ovarian cancer.

Key words: B7-H3, B7-H4, immune checkpoints, lymphocyte-activation gene 3, ovarian cancer, T-cell immunoglobulin and mucin-domain containing-3

BACKGROUND

Ovarian cancer currently ranks fifth in cancer-related deaths among women with an estimated 238,700 cases and 151,900 deaths.[1,2] Most patients are diagnosed in advanced disease, and the standard treatment is surgical debulking followed by platinum-based chemotherapy.[3] However, the 5-year relative survival of ovarian cancer was still poor[4] and overall survival is <4 years.[5-7] New valid therapeutic strategies are needed to improve the outcome of ovarian cancer patients. Immune checkpoints have become the focus of efforts as cancer immunotherapy recently.[8] Programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), and others are molecules involved in immune checkpoints. Monoclonal antibodies blocking some of these checkpoints such as CTLA-4 and PD-1 were approved for treating metastatic melanoma and other malignancies.[8-11] Additional checkpoint molecules such as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG3), B7-H3, and B7-H4 have been identified recently.[12-15] However, these immune checkpoints have been poorly studied in ovarian cancer. Here, we review the various checkpoint checkpoints that are in the clinic and their particular importance in ovarian cancer.

LAG3

LAG3 protein belongs to immunoglobulin (Ig) superfamily and contains four extracellular Ig-like domains. LAG3 was predicted to be highly structurally homologous to CD4 with four extracellular Ig superfamily-like domains.[16] LAG3 is mostly expressed on activated human T and NK cells,[17] small percentage (~18%) expressed on γδ T cells, and is also expressed on NK cells (~10%) and invariant natural killer T cells. Under physiological conditions, LAG3 is an activation marker for CD4+ and CD8+ T cells.[18] LAG3 coexpression with PD-1 correlates with a state of T-cell dysfunction in many human patient tumors. LAG3 is highly expressed on regulatory T-cells (Tregs) found in peripheral blood, tumor-involved lymph nodes, and within tumor tissue isolated from patients with advanced (Stages III and IV) melanoma and colorectal cancer.[19,20] In ovarian cancer, Matsuzaki *et al*. assessed the phenotype and function of NY-ESO-1-specific CD8+ T cells derived from peripheral blood lymphocytes, tumor-infiltrating lymphocytes, and tumor-associated lymphocytes of epithelial ovarian cancer patients with NY-ESO-1-expressing tumors (NY-ESO-1 is a "cancer-testis" antigen frequently expressed in epithelial ovarian cancer), with or without humoral immunity to NY-ESO-1. They found tumor-infiltrating NY-ESO-1-specific CD8+ T cells expressed high levels of

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PD-1, with some coexpressing LAG3.[21] There are currently some LAG3 modulating agents that have entered the clinic as anticancer therapeutics. Three different LAG3-specific mAbs have been developed for the treatment of cancer; BMS-986016 (Bristol-Myers Squibb, fully human IgG4), LAG525 (Novartis, humanized IgG4), and MK-4280 (Merck).[22] Since preclinical evidence supporting promising synergy with PD-1 blockade, clinical trial development of antagonistic LAG3 mAbs has expanded considerably recently.[23]

B7-H4

B7-H4 is a member of B7 family whose extracellular domain has approximately 25% homology with other B7 molecules. B7-H4 which also can be found in many peripheral non-immune tissues and is believed to be implicated in both costimulatory and coinhibitory pathways.[24] B7-H4 overexpression has been found in multiple solid malignancies including renal cancer,[25] breast,[26] and so on. Simon *et al*. found that B7-H4 was overexpressed in late stage ovarian cancers when low expression in normal ovaries and in benign tumors.[27] *In vitro* and *in vivo* studies showed that B7-H4 expression was upregulated in ovarian carcinoma cell lines and ovarian cancer patients. Knock-downing B7-H4 led to increased tumor cell apoptosis.[28] Kryczek *et al*. showed that ovarian tumor and associated macrophages expressed B7-H4, and tumor B7-H4+ macrophages and CD4+ CD25+ FOXP3+ Tregs suppressed tumor-associated antigen-specific T-cell immunity. Moreover, Treg cells may convey the suppressive activity to antigen-presenting cells through B7-H4 induction in human ovarian cancer.[29]

B7-H3

B7-H3 is another member of B7 family of immune-regulatory ligands that are thought to attenuate peripheral immune responses through coinhibition. B7-H3 is aberrantly overexpressed in many types of cancer, and such upregulation is generally associated with a poor clinical prognosis. Zang *et al.* examined the expression of B7-H3 in 103 ovarian borderline tumors and carcinomas and studied associations with clinical outcome. They found 93% of these ovarian tumors express B7-H3. B7-H3 was also expressed in the endothelium of tumor-associated vasculature in 44% of patients, including 78% of patients with high stage tumors (FIGO Stages III and IV), nearly all of which were high-grade serous carcinomas. Analysis of cumulative survival time and recurrence incidence revealed that carcinomas with B7-H3-positive tumor vasculature were associated with significantly shorter survival time and a higher incidence of recurrence. Their results suggested that ovarian borderline tumors and carcinomas aberrantly express B7-H3 and that B7-H3-positive tumor vasculature is associated with high-grade serous histological subtype, increased recurrence, and reduced survival.[30]

TIM-3

TIM-3, a member of Ig superfamily, is expressed on fully differentiated Th1 lymphocytes, but not on Th2 cells.[31] By interacting with its ligands, TIM-3 induces the apoptosis of T cells and functional inhibition in tumor tissues.[32-34] The ectopic TIM-3 expression has been demonstrated as an independent prognostic factor for some tumors such as cervical cancer,[35] lung cancer,[36] prostate cancer,[37] and renal cancer.[38] Further, anti-TIM-3 displayed prophylactic and therapeutic activity in multiple, preclinical cancer models.[39] In ovarian cancer, expression of TIM-3 was significantly increased in both CD4+ and CD8+ T cells, and patients who had recurrent ovarian cancer had a higher proportion of TIM-3+ CD4+ T cells than when they were newly diagnosed.[40] TIM-3+ T cells presented all features of functional exhaustion and correlated with poor disease outcome. TIM-3 constitutes prognostically relevant biomarkers of active and suppressed immune responses against high-grade serous ovarian carcinoma.[41]

CONCLUSIONS

Immune checkpoint therapy has become a welcome and important addition to the current anticancer treatment. Besides CTLA-4 and PD-1, immune checkpoints such as LAG3, TIM-3, B7-H3, and B7-H4 have shown promise for passive immunotherapy, particularly in ovarian cancer. More preclinical and clinical trials are needed to prove the effectiveness.

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