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Review Article

Ovarian cancer and the immune system — The role of targeted therapies

Taylor B. Turner [a,*], Donald J. Buchsbaum [b], J. Michael Straughn Jr. [a], Troy D. Randall [c], Rebecca C. Arend [a]

[a] Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
[c] Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA

HIGHLIGHTS

- Ovarian cancer therapies do not account for interactions with the immune system.
- Molecular targets can augment immune response or negate immunosuppression.
- FDA approved immunomodulatory agents show promise in ovarian cancer.

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ABSTRACT

The majority of patients with epithelial ovarian cancer are diagnosed with advanced disease. While many of these patients will respond initially to chemotherapy, the majority will relapse and die of their disease. Targeted therapies that block or activate specific intracellular signaling pathways have been disappointing. In the past 15 years, the role of the immune system in ovarian cancer has been investigated. Patients with a more robust immune response, as documented by the presence of lymphocytes infiltrating within their tumor, have increased survival and better response to chemotherapy. In addition, a strong immunosuppressive environment often accompanies ovarian cancer. Recent research has identified potential therapies that leverage the immune system to identify and destroy tumor cells that previously evaded immunosurveillance mechanisms. In this review, we discuss the role of the immune system in ovarian cancer and focus on specific pathways and molecules that show a potential for targeted therapy. We also review the ongoing clinical trials using targeted immunotherapy in ovarian cancer. The role of targeted immunotherapy in patients with ovarian cancer represents a field of growing research and clinical importance.

Contents

* Corresponding author at: Department of Obstetrics and Gynecology, University of Alabama at Birmingham, 1700 6th Avenue South, Room 10250, Birmingham, AL 35233, USA.
E-mail address: taylorturner@uabmc.edu (T.B. Turner).

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1. Introduction

Epithelial ovarian cancer (EOC) remains the deadliest gynecologic malignancy in the United States, with an estimated 21,000 new cases and 14,000 deaths in 2015 [1]. Advances in traditional cytotoxic chemotherapy such as intraperitoneal administration and dose-dense therapeutic regimens are improving response rates, as are novel agents like bevacizumab, but these treatments are failing to significantly affect overall survival [2]. Moreover, patients often develop resistance to chemotherapy. Thus, there is an urgent need to identify novel treatments, such as immune-directed therapies, to replace traditional cytotoxic chemotherapy. The objective of this review is to discuss the immune response in ovarian cancer and to review targeted therapies currently used to enhance the immune response against EOC. This focus precludes significant discussion regarding viral and cellular based therapies, the latter having been recently reviewed [3].

2. The immune system and cancer

Although one might assume that the immune system cannot recognize or eliminate cancer cells because they are a form of "self", rather than foreign invaders like viruses or bacteria, new data clearly show that immunodeficient mice are much more susceptible to malignancy [4,5], implying that adaptive immunity is important for keeping tumor cells in check. In fact, a variety of immune cells, particularly T cells and natural killer (NK) cells, are important for the identification and cytotoxic elimination of tumor cells.

T cells, which are broadly distinguished by cell surface expression of either CD8 or CD4, recognize peptide antigens that are presented by major histocompatibility complex type I (MHC-I) or MHC-II proteins, respectively. Classic tumor antigens are presented by MHC-I proteins, which typically display peptides from endogenous, cytosolic proteins. In contrast, MHC-II proteins typically display peptides derived from exogenous proteins that a cell has acquired via the phagocytic and endosomal pathways. Essentially all cells in the body express MHC-I proteins and can present antigens to activated CD8 T cells, whereas, under normal circumstances, only a handful of cells, particularly B cells, macrophages and dendritic cells, normally express MHC-II proteins and present antigens to CD4 T cells. Importantly however, the initial activation of naive T cells (both CD4 and CD8) occurs almost exclusively through interactions with antigen-presenting dendritic cells [6].

CD8 and CD4 T cells also differ in their functional roles. CD8 T cells are the classic "killers" of the immune system and, upon recognition of specific antigens in MHC-I, kill target cells via the production of cytokines, such as tumor necrosis factor (TNF), and interferon-γ (IFN-γ), and enzymes like granzyme-B and perforin. In contrast, CD4 T cells are rarely cytotoxic and instead promote the recruitment and activation of other cells. For example, CD4 T cells are necessary for the differentiation of antibody-producing B cells, the activation of macrophages and dendritic cells, and the recruitment of inflammatory cells [7] , including other T cells. Conversely, under some circumstances, CD4 T cells can also act as immune suppressive regulatory T cells (Tregs), which will be discussed later.

NK cells are also important for the recognition and cytotoxic elimination of tumor cells. NK cells are part of the innate immune system and are capable of direct cellular cytotoxicity based on cell surface ligand-receptor interactions with target cells. Importantly, NK cells have inhibitory receptors that recognize MHC-I molecules [8]. As a result, NK cells are typically inhibited from killing "normal" cells. However, they are potent killers of cells that have lost the expression of MHC-I, which often occurs due to infection or during the process of tumorigenesis [9]. Like CD8 T cells, NK cells are potent producers of TNF, IFN-γ, granzyme-B and perforin [10]. Thus, the combined activities of CD8 T cells and NK cells are important for the cytotoxic elimination of tumor cells.

Despite the ability of immune cells, like CD8 T cells and NK cells, to recognize and eliminate tumor cells, tumors often grow seemingly unchecked in immunocompetent individuals. This phenomenon is due to a variety of effects, including poor immunogenicity of some tumors [11], immunosuppression [12], and immunoediting [13]. One way in which tumors can evade immunosurveillance is by creating a local or systemic immunosuppressive environment. For example, tumor cells can produce vascular endothelial growth factor (VEGF), which aids tumor growth by promoting angiogenesis and by inhibiting the ability of dendritic cells to activate T cells [14]. Similarly, tumor cells can produce transforming growth factor–β (TGF-β), which can directly promote tumor cell growth, suppress CD8 T cell activation and promote the differentiation of regulatory CD4 T cells [15]. Moreover, enzymes like indoleamine 2,3-dioxygenase (IDO), can inhibit the immune response by depleting tryptophan and promoting the accumulation of kynurenine, which can inactivate NK cells and promote Treg differentiation [16]. Tumor cells may express inhibitory ligands, like programmed death ligand 1 (PD-L1), which binds to the inhibitory receptor, PD-1, on CD4 and CD8 T cells and inhibits their proliferation and effector functions [17]. Importantly, many of the same mechanisms that impair conventional CD4 and CD8 T cell activation also promote the accumulation or differentiation of immunosuppressive Tregs, which reinforce the immunosuppressive environment [18].

Even in immunogenic tumors, a process known as immunoediting may occur that leads to the selective outgrowth of tumors that escape immune control [19]. Given that tumors are made up of populations of genetically unstable, rapidly proliferating cells, a portion of these cells may be recognized by the immune system and eliminated from the population, leaving the cells that are less easily recognized or more difficult to eliminate. In fact, the immune system often maintains an *equilibrium* with tumor cells that may persist for extended periods of time and prevent any clinical sequelae. In this phase, the most immunogenic cells are continually removed, a process that shapes and refines the remaining tumor population until finally a population of tumor cells *escapes* immunologic control and grows unchecked [18]. The escape from immunologic control can occur via several mechanisms, including loss of tumor antigen expression [20], loss of MHC-I expression [9], or failure of the intracellular antigen presentation pathway [21]. Tumor cells may also acquire increased resistance to cytotoxicity via the de novo expression of oncogenes or mutations in tumor suppressor genes that increase resistance to apoptosis [22]. Understanding the role each of these pathways play in different malignancies is key to developing targeted immunologic therapies.

3. The immune response in ovarian cancer

3.1. Tumor infiltrating lymphocytes

Similar to other solid tumors , the role of the immune response in ovarian cancer is well documented [23–25]. A selection of key studies is provided in Table 1. For example, there is a positive correlation between the number of tumor infiltrating lymphocytes (TILs) and overall