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Review

A review of B7-H3 and B7-H4 immune molecules and their role in ovarian cancer

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HIGHLIGHTS

- B7 molecules are involved in tumor immunogenicity and cancer development.
- B7-H3 has been associated with poor prognosis in a number of cancer types, including ovarian cancer.
- B7-H3 and B7-H4 have been found to be overexpressed on ovarian cancer tumors and are associated with shortened survival.

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ABSTRACT

A number of members of the B7 superfamily of ligands have been implicated in tumor immunogenicity and cancer development. Two of these recently characterized ligands, B7-H4 and B7-H3, have been linked to ovarian tumors. B7-H4 is consistently overexpressed in ovarian tumor specimens, and its tissue and serum levels have been found to be a potential biomarker for ovarian cancer, either alone or in combination with CA125. More recently, B7-H3 has been found to be overexpressed in a large series of ovarian cancer tumor specimens and similar to other types of carcinomas, B7-H3 overexpression has been correlated with poor survival. On the basis of the results obtained by knocking down B7-H3 protein using siRNA, researchers have suggested that blocking the action of B7-H3 could reduce tumor growth, metastatic potential, and improve survival. Because siRNA knock-down is not an ideal clinical therapeutic vehicle, additional studies using antibody-mediated suppression of the B7-H3 protein are necessary to fully evaluate the clinical potential of this molecule as a therapeutic target.

Contents

Introduction

T-lymphocytes play an integral role in the adaptive immune response, and their ability to recognize a vast selection of foreign and native antigens is essential to maintain homeostasis and self-tolerance.

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The role of T-cells in anti-tumor immunity is complex. Often their interplay with B-cells can be both supportive and inhibitory, a dichotomy that leads to difficulty ascertaining the exact mechanism of tumor development and suppression. T-cell activation and proliferation are accomplished through both antigen-dependent and antigen-independent pathways. Antigen-dependent T-cell proliferation requires an antigen-specific receptor on the T-cell recognizing the major histocompatibility complex (MHC) on an antigen presenting cell (APC). The antigen-independent pathway involves B7-1/B7-2:CD28/cytotoxic T lymphocyte-associated protein 4 (CTLA-4) signaling, a well-studied co-stimulatory pathway. In this pathway, B7-1 on APCs binds to CD28 on T-cells, and this interaction leads to T-cell proliferation and IL-2 production [1]. T-cell inhibition is also multi-factorial. The same co-stimulatory process that leads to T-cell proliferation can serve as a self-regulatory mechanism; binding of CTLA-4 to B7 molecules inhibits IL-2 production and down-regulates T-cell proliferation [2]. Inhibition can also be induced by CD4 T-cells, known as T-regulatory (Treg) cells. These cells express high levels of CD25 and FOXP3. FOXP3 has been recognized as a marker for Treg activity in the mouse model, and these cells have the ability to actively inhibit CD4, CD8, dendritic cells (DCs), natural killer (NK) cells, and B-cells [3]. One of the cell surface markers associated with Treg function is CTLA-4, which interacts with IL-10 and TGF-β especially in the context of disease. Tregs are recruited to the tumor environment via cytokine, primarily CCL_{22}. Expansion of Treg cells has been correlated with poor prognosis in many solid cancer types, including ovarian cancer. The poor prognosis is correlated to decreased numbers of $CD8^+$ T cells, and the subsequent promotion of tumor growth [4]. Treg cells have also been shown to increase VEGF and angiogenesis [5].

The role of the tumor microenvironment is critical for tumor growth. It is composed of dysfunctional immune cells that have been reprogrammed to evade tumor immunity. The process of evasion is accomplished by both the presence of dysfunctional APCs including dendritic cells and macrophages, and the increased expression of inhibitory B7 molecules by these aberrant APCs, stromal and tumor cells [6]. This "immune-escape" theory of tumors involves Treg cells inducing the production of IL-6 and IL-10 by macrophages, which subsequently cause APC to express B7-H4 via autocrine and paracrine mechanisms [7]. Additionally, these APC cells secrete high levels of TGF-β, which in turn increase B7 expression and T-cell inhibition via interference with the cell cycle. It is this interaction between TGF-β and B7 molecules that has identified the B7 homologues as potential regulators of anti-tumor immunity (Fig. 1) [8].

B7 family

In recent years, there have been new discoveries of co-stimulatory molecules within the B-family of ligands, including B7-H1 (programmed death-1 ligand-1), B7-DC (programmed death-1 ligand-2), PD-1 (programmed death-1), ICOS (inducible costimulator), ICOSL (ICOS-ligand), B7-H4, and B7-H3. These new B7 molecules have been implicated in the development and suppression of many solid tumors including ovarian cancer [9].

There are seven well-described members of the B7 superfamily of ligands (Table 1). They are transmembrane or glycosylphosphatidylinositol (GPI)-lined proteins containing extracellular IgV and IgC domains. B7-H3 is unique in that the human form contains two extracellular tandem IgV–IgC domains. They also contain intracytoplasmic domains which are involved with phosphorylation sites in signaling pathways.

The B7 family can be grouped into 3 categories based on their function [10]. The first group consists of B7-1 (CD80) and B7-2 (CD86). These molecules bind to CD28 and CTLA-4 (CD152) on T-cells and are involved in co-stimulation and co-inhibition, respectively. They are expressed on lymphoid cells, including B-cells, T-cells, dendritic cells (DC) and monocytes. This group also contains B7-H2 (also referred to as ICOS-L), which binds ICOS and is involved in co-stimulatory pathways. In addition to being expressed on lymphoid cells, they are also found in lung, liver, kidney and testicular tissue.

The second group consists of B7-H1 (PD-L1) and B7-DC (PD-L2), which constitute the ligands of the programmed cell death-1 receptor-ligand complex and are involved in peripheral immune tolerance and T-cell impairment. Their function and expression are modulated by cytokines, such as IL-4, IL-13 and INF-γ. They can also

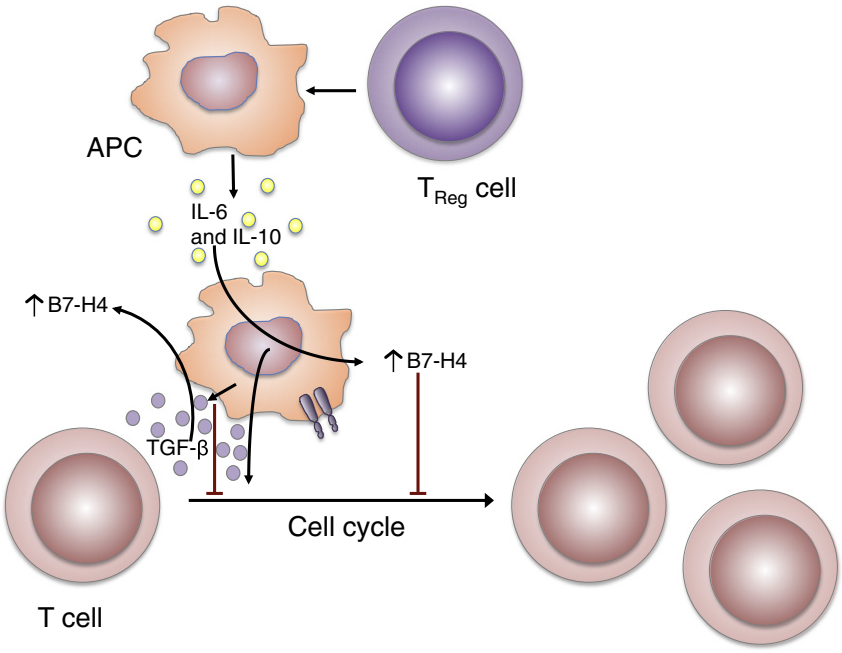

Fig. 1. The "immune-escape" theory of tumors involves the B7-presenting tumor-associated APC producing high levels of IL-6 and IL-10 after transformation by T_{Reg} cells. This leads to increased B7-H4 expression, which in turn leads to T-cell inhibition via interference with the cell cycle. Additionally, these APCs secrete high levels of TGF-β, which in turn leads to increased B7-H4 expression.