ELSEVIER

Seminars in Cancer Biology 17 (2007) 288–298

seminars in
CANCER BIOLOGY

www.elsevier.com/locate/semcancer

Review

Inhibitory costimulation and anti-tumor immunity

Natalia Martin-Orozco, Chen Dong *

Department of Immunology, The University of Texas M.D. Anderson Cancer Center, TX, USA

Abstract

Costimulation was originally shown to be important in T-cell activation and effector differentiation. Recent characterization of B7/butyrophilin and members of the CD28 superfamily has revealed a large number of negative costimulatory molecules that dampen T-cell activation and regulate immune tolerance. Some of these molecules have been shown to be upregulated in the tumor microenvironment and may serve as potential targets for augmenting anti-tumor immunity. In this article, we summarize recent developments in the field of inhibitory costimulation and discuss the future direction of therapeutic manipulation of inhibitory costimulation in tumor immunotherapy.

Keywords: Costimulation; B7; Anti-tumor immunity; Tolerance

Contents

1. Introduction

Stimulation of T-cells by peptides presented on MHC molecules is accompanied by an array of cell-surface costimulatory molecules that are present on antigen-presenting cells (APC), which engage their corresponding receptors on T-cells. For many years, costimulation has underscored the "two-signal" theory. This theory states that: (1) to obtain optimal T-cell activation, costimulation would complement the signal provided by MHC-peptide to ensure productive T-cell activation leading to the effector function; and conversely, (2) the lack of costimulation would result in T-cell tolerance or "anergy" [1]. CD28 on naïve T-cells is by far the most important costimulatory receptor

* Corresponding author at: Department of Immunology, Unit 906, 7455 Fannin St., Houston, TX 77030, USA. Tel.: +1 713 563 0406; fax: +1 713 563 0406.
E-mail addresses: nmorozco@mdanderson.org (N. Martin-Orozco), cdong@mdanderson.org (C. Dong).

1044-579X/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcancer.2007.06.003

[2]. Naïve T-cells costimulated with anti-CD28 have been shown to greatly enhance proliferation and interleukin (IL)-2 production. Consistently, mice deficient in CD28 or both of its ligands (B7.1 and B7.2, hereafter referred to as B7-deficient mice) have been shown to be severely impaired in $CD4^+$ T-cell proliferation [3,4]. The expression of ICOS, a member of the CD28 family, on T-cells has also been demonstrated [5,6]. Analysis of mice deficient in ICOS or its ligand, B7h, revealed that this pathway, although not globally required for $CD4^+$ T-cell activation and effector differentiation, regulates their selective effector function [7–10]. CD28 and ICOS pathways have a synergistic yet redundant function. In recent studies, deficiencies in both pathways led to complete T-cell tolerance *in vitro* and *in vivo* [11,12].

Accompanying genomic and cDNA sequencing projects, a number of novel B7-like molecules have been discovered and characterized. It has become clear that numerous inhibitory pathways exist to dampen T-cell function (Table 1). In this review, we will first summarize reports in the current literature about the biology of these pathways and their presence in tumors and then discuss their potentials as targets for cancer therapy.

2. Negative costimulatory molecules

2.1. Cytotoxic T-lymphocyte-associated antigen 4

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a homologue of CD28 that binds to B7.1 (CD80) and B7.2 (CD86) with 10-fold higher affinity than CD28 [13]. Unlike CD28, which is expressed on the surface of naïve T-cells, CTLA-4 is not found in naïve T-cells but is strongly induced on activated T-cells. The role of CTLA-4 as a negative regulator was clearly shown in CTLA-4-deficient mice, which display polyclonal T-cell activation and lymphoproliferative disorder that results in neonatal lethality [13]. In addition, a number of studies have shown a critical role of CTLA-4 in induction of peripheral tolerance [14]. Some recent additional studies have implicated T-cell suppressor function mediated by CTLA-4 expressed by $CD4^+CD25^+$ regulatory T (Treg) cells. Blockade of CTLA-4 with an antagonistic antibody abrogates Treg function [15]. Another possible way whereby CTLA-4 inhibits T-cell function is through reverse signaling of B7.1 and B7.2 in dendritic cells (DC). This unique pathway was reported to induce tryptophan catabolism by upregulating the expression of indoleamine 2,3-dyoxygenase (IDO) in DC, which subsequently inhibits T-cell proliferation [16,17].

2.2. PD-1 and its ligands

Programmed cell death-1 (PD-1) is another transmembrane glycoprotein belonging to the CD28 superfamily [18]. PD-1 is expressed on activated T-cells, B-cells, and monocytes [19,20] and at low levels in natural killer (NK) T-cells [21]. The extracellular region of PD-1 consists of a single immunoglobulin (Ig)V domain with 23% identity to the equivalent domain in CTLA-4 [22]. Originally isolated as an apoptosis-associated gene [18], it has become clear that PD-1 provides a crucial negative costimulatory signal to T- and B-cells. PD-1 regulation of peripheral tolerance was firmly demonstrated in PD-1-deficient mice, which develops autoimmune diseases. Interestingly, the genetic background influences the autoimmune phenotype. For example, knockout of *Pdcd-1* gene on the C57BL/6 background leads to arthritis and lupus-like glomerulonephritis [23], whereas in Balb/c mice knockout of *Pdcd-1* yields dilated cardiomyopathy with the presence of elevated titers of anticardiac troponin I auto-antibodies [24,25].

PD-1 has two ligands belonging to the B7 superfamily: PD-L1 (B7-H1) and PD-L2 (B7-DC) [26–29]. PD-L1 mRNA, broadly expressed in different human and mouse tissues, such as heart, placenta, muscle, fetal liver, spleen, lymph nodes, and thymus for both species as well as liver, lung, and kidney in mouse only. In humans, PD-L1 protein expression has been found in human endothelial cells [30–32], myocardium [33], syncyciotrophoblasts [33,34], resident macrophages of some tissues, or in macrophages that have been activated with interferon (IFN)-γ or tumor necrosis factor (TNF)-α [28], and in tumors [35]. In the mouse, PD-L1 protein expression is found in heart endothelium, islets cells of the pancreas, small intestines, and placenta [36]. In mouse hematopoetic cells, PD-L1 is expressed constitutively on T-cells, B-cells, macrophages, and DCs and can be upregulated upon activation [20]. In contrast to PD-L1, PD-L2 mRNA, and protein expression do not correlate so well.

Table 1
B7 family members

Ligand	Expression	Receptor	Function
B7.1/B7.2 (CD80/CD86)	Activated APC	CD28/CTLA-4	T-cell activation and tolerance
B7h (B7RP1, ICOS-L, B7-H2)	B-cells, macrophages, and non-lymphoid tissues	ICOS	T-cell activation
B7-H1 (PD-L1)/B7DC (PD-L2)	APC and non-lymphoid tissues	PD-1	Inhibition of T-cell activation and tolerance
B7-H3	Lymphoid and non-lymphoid tissues	Unknown	Inhibition of T-cell activation
B7S1 (B7-H4, B7x, VTCN1)	Lymphoid and non-lymphoid tissues	Unknown	Inhibition of T-cell activation
HVEM	Lymphoid and non-lymphoid tissues	BTLA	Inhibition of T-cell and B-cell activation
BTNL2	Lymphoid and non-lymphoid tissues	Unknown	Inhibition of T-cell activation
VSIG4	Macrophages and non-lymphoid tissues	Unidentified receptor, Complement C3b/iC3b	Inhibition of T-cell activation
B7S3	Lymphoid and non-lymphoid tissues	Unknown	Inhibition of T-cell activation

Abbreviations: Antigen-presenting cells, APC; cytotoxic T-lymphocyte-associated antigen 4, CTLA-4; inducible T-cell costimulator, ICOS; programmed cell death, PD; Herpes virus enter mediator, HVEM; B- and T-lymphocyte attenuator, BTLA; V-set and Ig domain containing-4 (VSIG4).