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- 1 Historical evolution, overview, and therapeutic manipulation of co-stimulatory molecules

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Historical evolution, overview, and therapeutic manipulation of co-stimulatory molecules

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Abstract

Co-stimulatory molecules are key mediators in the regulation of immune responses and knowledge of its different families, structure, and functions has improved in recent decades. Understanding the role of co-stimulatory molecules in pathological processes has allowed the development of strategies to modulate cellular functions. Currently, modulation of co-stimulatory and co-inhibitory molecules has been applied in clinical applications as therapeutic targets in diseases and promising results have been achieved.

Key Words: Co-stimulatory molecules; Immune modulation; Monoclonal antibodies; Biological therapy; Autoimmune diseases; Oncological diseases

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Core Tip: Several reviews of co-stimulatory molecules have been published, however, this review summarizes the historical aspects, the cellular and molecular mechanisms of the different families of costimulatory molecules implied in processes of health and disease. All of this knowledge has been applied to develop different drugs targeting costimulatory molecules in different diseases like cancer and autoimmune diseases.

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INTRODUCTION

Regulation of the immune response is a crucial process in the initiation and control of inflammatory phenomena. Various mechanisms capable of regulating T cell activation have been described. Co-stimulatory molecules were initially described as accessory signals present in antigen-presenting cells (APCs) that interacted with T cells during the immunological synapse[1]. They comprise a diversity of glycoproteins expressed in the membrane of APCs, and they interact with other glycoproteins that function as their receptors on T cells, modulating in a positive or negative way the activation, proliferation, differentiation, and function of T cells[2]. In recent decades, advances in the knowledge of co-stimulatory molecules and the development of biological drugs allowed a therapeutic targeting of co-stimulatory molecules in distinct diseases[3].

A BRIEF HISTORY OF CO-STIMULATORY MOLECULES

A two-signal model of T cell activation was first proposed in the second half of the 1960s. The two signals were antigen recognition by an antigen receptor and the interaction with co-stimulatory molecules. Although the mechanisms were not known, the model proposed that in the absence of a second signal or "co-stimulation," the T cell would enter a state of paralysis or inactivation[4,5]. By the second half of the 1980s, a series of investigations had experimentally demonstrated the existence of co-stimulatory molecules and their participation in T cell activation[6-9]. The findings resulted in the description of a diversity of molecules and the investigation of their function in different disease models, which led to therapeutic applications. One example is the 2018 Nobel Prize in Physiology and Medicine, awarded to Tsuku Honjo and James P Allison, for their contributions to the discovery of cytotoxic T lymphocyte-associated antigen (CTLA)-4 and programmed death (PD)-1 protein and the development of methods of molecular blockade for the treatment of oncological diseases[10-12].

OVERVIEW OF ANTIGEN PRESENTATION AND INVOLVEMENT OF CO-STIMULATORY MOLECULES

APCs are part of the innate immune system and act as an interface between antigen recognition and the adaptive response of T cells during antigen presentation[3]. Activation of T cells requires the appropriate activation and integration of three signals. The first signal is the antigen, which is presented in the context of the major histocompatibility complex, and its recognition by the T cell receptor (TCR). The first signal is not sufficient to activate T cells. Activation continues with a second signal that involves the participation of surface molecules expressed on dendritic cells that interact with their respective receptors on the T cell. The third signal involves the production of cytokines, which not only favor the activation state but also promote the polarization of T cells into their various helper/cytotoxic subpopulations[3,13] (Figure 1). In that dynamic microenvironment, the spatiotemporal expression of various co-stimulatory molecules on dendritic cells and T cells, as part of the second signal, is the key to regulating T cell activation, inhibition, survival, and polarization.

Activating and inhibitory signals

Co-stimulatory molecules are transmembrane glycoproteins that induce activation or inhibition cascades that enhance or diminish TCR signaling[14,15]. Stimulatory, or activating signals (co-stimulation by CD28 or CD40), lead to the production of growth factors, cell expansion, and survival. Inhibitory signals (co-inhibition by PD1 or CTL-4) attenuate TCR-induced signals, resulting in decreased cell activation, inhibition of growth factor production, inhibition of cell cycle progression, and in some cases, promotion of cell death[14].

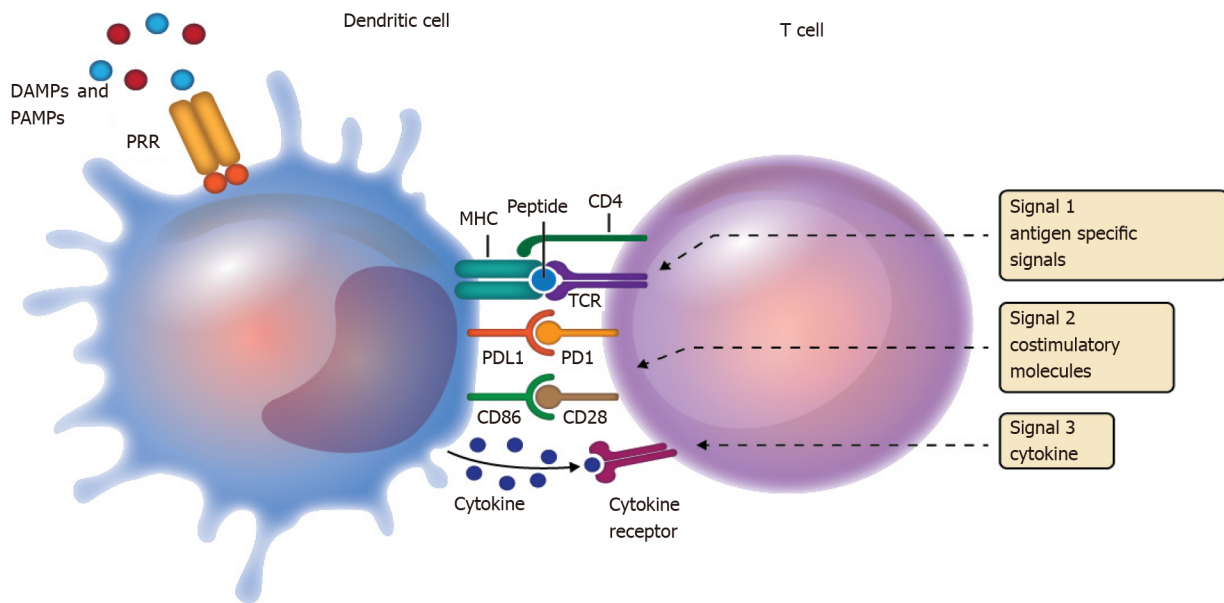


Figure 1 Overview of antigen presentation and the three-signal model. The three-signal model proposes: (1) Antigen presentation to the T cell receptor by the major histocompatibility complex; (2) Interaction of co-stimulatory molecules with their receptors; and (3) Cytokine production and recognition by the cytokine receptors of T cells. DAMPs: Damage-associated molecular patterns; PAMPs: Pathogen-associated molecular patterns; PD1: Programmed death-1; PDL1: Programmed death ligand 1; PRR: Pattern recognition receptor.

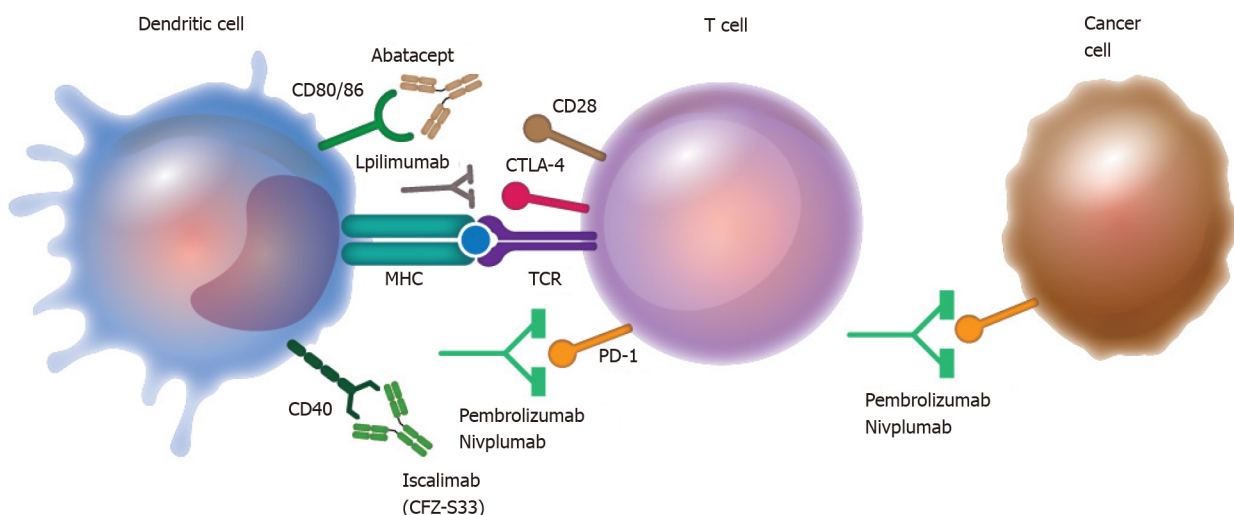


Figure 2 Therapeutic manipulation of co-stimulatory molecules. Biological drugs have been developed to target co-stimulatory molecules and promote or inhibit their functions in distinct diseases. For example, the fusion protein abatacept blocks CD80/CD86 to prevent interaction with CD28; mAb icalimab blocks CD40, ipilimumab blocks cytotoxic T lymphocyte antigen-4, and pembrolizumab blocks programmed death-1 (PD-1). These strategies have been implemented to modulate co-stimulatory molecule functions in immune and cancer cells. MHC: Major histocompatibility complex; TCR: T cell receptor.

Families of co-stimulatory molecules

Co-stimulatory molecules are divided into two main families by their molecular structure. The first (Table 1) is the immunoglobulin superfamily which includes CD226, the CD2/signaling lymphocytic activation molecule family, T cell immunoglobulin and mucin (TIM) family, butyrophilin (BTN) family, and leukocyte-associated immunoglobulin-like receptor (LAIR) family. Because of its historical relevance, the most studied is the B7 family, which includes CD80, CD86, and its receptor CD28. The second (Table 2) is the tumor necrosis factor superfamily (TNFR SF), which includes three subfamilies, the divergent type (OX-40, CD27, glucocorticoid-induced TNFR-related protein), the S-type (CD267), and the conventional type [FAS, herpes virus entry mediator, receptor activator of nuclear factor kappa-B (RANK), and CD40]. CD40 and its ligand CD40L are the most investigated co-stimulation molecules of the TNFR SF[3].

Table 1 Immunoglobulin super family co-stimulatory molecules

IgSF co-stimulatory molecules	Function	Cells expressing the receptor	Ligand	Cells expressing the ligand
CD28	Activation	Constitutive in T cells	CD80, CD86	CD80: Inducible in dendritic cells, monocytes, B and T cells. CD86: Constitutive in dendritic cells, monocytes, B and T cells
ICOS (CD278)	Activation	Inducible in T, B, and NK cells	ICOSL	Constitutive in macrophages, dendritic cells, B and T cells
CTLA-4 (CD152)	Inhibition	Inducible in T cells	CD80, CD86	CD80: Inducible in dendritic cells, monocytes, B and T cells. CD86: Constitutive in dendritic cells, monocytes, B and T cells
PD-1 (CD279)	Inhibition	Inducible in T, and B cells, macrophages	PD-L1, PD-L2	PD-L1: Constitutive in dendritic cells, B and T cells. PD-L2: Inducible in dendritic cells and monocytes
PD-1H (VISTA)	Inhibition	Monocytes, neutrophils, T cells	Unknown	Unknown
BTLA (CD272)	Inhibition	B and T cells	HVEM, UL144	Monocytes, B and T cells
B71 (CD80), B72 (CD86)	Activation/Inhibition	CD80: Inducible in dendritic cells, monocytes, B and T cells. CD86: Constitutive in dendritic cells, monocytes, B and T cells	CD28, CTLA-4	CD28: Constitutive in T cells. CTLA-4: Inducible in T cells
B7H1 (CD274, PDL1)	Inhibition	Constitutive in dendritic cells, monocytes, B and T cells	PD-1, B71	PD-1: Inducible in macrophages, B and T cells. CD80: Inducible in dendritic cells, monocytes, B and T cells

BTLA: B- and T lymphocyte attenuator; CTLA: Cytotoxic T lymphocyte antigen; HVEM: Herpes virus entry mediator; ICOS: Inducible T cell co-stimulator; ICOSL: Inducible T cell co-stimulator ligand; PD-1: Programmed death-1; PD-L: Programmed death ligand; PD-1H: Programmed death-1 homolog; VISTA: V domain Ig suppressor of T cell activation.

Co-stimulatory molecules and their study in human disease

The involvement of co-stimulatory molecules in clinical conditions has been explored. Mutations in ICOSL, CD40, or C267 have been associated with immunodeficiencies; increased expression of CD86, CD28, CD27, and CD70 has been reported in autoimmune diseases and allergies[16-23]. Some of the most interesting findings are summarized in Tables 3 and 4.

Therapeutic application of co-stimulatory or co-inhibitory molecules

Numerous scientific studies have shown the involvement of co-stimulatory molecules in the regulation of the inflammatory process[3]. Subsequently, both experimental trials in various disease models and preclinical trials have demonstrated promising results achieved by the therapeutic manipulation of these molecules[24,25]. The preclinical results support their application at the clinical level either by inhibiting the function of activating co-stimulatory molecules to promote tolerogenic functions or by inhibiting inhibitory co-stimulatory molecules to promote pro-inflammatory functions.

Blockade of the co-inhibitory molecules PD1 and CTLA-4 by the monoclonal antibodies pembrolizumab, ipilimumab, and nivolumab is a therapeutic indication in cancer treatment, particularly melanoma. On the other hand, therapeutic approaches for autoimmune diseases have exploited the blockade of the co-stimulatory molecules CD80/CD86 by abatacept or CD40 by iscalimab. In both cases, co-stimulatory molecule-targeted therapies have shown promising results[26-32] (Figure 2 and Table 5).

CONCLUSION

Challenging limitations need to be overcome before these therapeutical tools are approved for clinical use[33]. Nevertheless, understanding the function and the possibility of therapeutic manipulation of co-stimulatory molecules represents a milestone for immunology and pharmacology. The knowledge gained from the study of co-stimulatory molecules has allowed a deeper understanding of the pathophysiology of many diseases. The therapeutic use of these molecules has been

Table 2 Tumor necrosis factor receptor super family co-stimulatory molecules

TNFR SF co-stimulatory molecules	Function	Cells expressing the receptor	Ligand	Cells expressing the ligand
OX40 (CD134)	Activation	Activated and regulatory T cells	OX40L	T cells, macrophages, endothelial cells, vascular smooth muscle cells, dendritic cells, tumor cells
CD27 (TNFR SF7)	Activation	T and B cells, NK cells	CD70	NK, T and B cells
GITR (CD357)	Activation	T cells	GITRL	T cells
CD30 (TNFR SF8)	Activation	T and B cells	CD30L	T cells
HVEM (CD270)	Activation	Monocytes, T and B cells	LIGHT, BTLA, CD160, LT α 3, HSV1gD	Monocytes and APCs
FAS (CD95)	Activation	NK and T cells	FASL	Dendritic cells, NK, T cells, neutrophils
CD40 (TNFR SF5)	Activation	All B-cell lineages except plasma cells, macrophages, activated monocytes, follicular dendritic cells, interdigitating dendritic cells, endothelial cells, fibroblasts	CD40L	Activated CD4+ T cells, some CD8+ T cells, $\gamma\delta$ T cells, basophils, platelets monocytes and mast cells
RANK (CD265)	Activation	Osteoclast and dendritic cells	RANKL	Osteoblasts, T cells
TACI (CD267)	Inhibition	B and plasma cells	BAFF, APRIL	Stromal cells, dendritic cells, and macrophages

APCs: Antigen-presenting cells; APRIL: A proliferation-inducing ligand; BAFF: B-cell activating factor; BTLA: B- and T lymphocyte attenuator; FASL: FAS ligand; GITR: Glucocorticoid-induced TNFR-related protein; HSV1gD: Herpes simplex virus-1 glycoprotein D; HVEM: Herpes virus entry mediator; LIGHT: TNFR14; LT3: Lymphotoxin-alpha 3; RANK: Receptor activator of nuclear factor kappa; TACI: Transmembrane activator and calcium-modulator and cyclophilin ligand interactor; TNFR SF: Tumor necrosis factor superfamily.

Table 3 Immunoglobulin super family co-stimulatory molecules studied in various diseases

Molecule	Disease	Alteration	Ref.
CD86	Rheumatoid arthritis	Increased expression in B cells	[16]
ICOSL	Combined immunodeficiency	Mutation	[17]
CTLA-4	Mycosis fungoides	Increased expression in T cells	[18]
CD28	Tuberculosis	Decreased expression in CD8+ and CD4+ T cells	[19]
CD28	Graves' disease	Increased expression in T cells	[20]

CTLA: Cytotoxic T lymphocyte antigen; ICOSL: Inducible T cell co-stimulator ligand.

Table 4 Tumor necrosis factor superfamily co-stimulatory molecules studied in various diseases

Molecule	Disease	Alteration	Ref.
CD27	Lupus erythematosus	Increased expression in plasmablasts	[21]
CD70	Lupus erythematosus	Increased expression in plasmablasts	[21]
CD40	Hyper IgM Syndrome	Mutations	[22]
CD30	Vernal Keratoconjunctivitis	Increased expression in T cells	[23]
CD267	Common variable immunodeficiency	Mutations	[24]

well exploited in autoimmune diseases and oncology, where they serve as effective adjuvants to conventional therapy. However, we should not exclude the potential that these molecules have in many other contexts. They will undoubtedly continue to be an area of great interest for research and drug development.

Table 5 Co-stimulatory molecule manipulation in various diseases

Disease	Therapeutic target	Manipulation	Outcome	Ref.
Brain metastases melanoma	PD-1 and CTLA-4	Blockade with mAbs (nivolumab + ipilimumab)	55% of treated patients reduced tumor size. 21% showed full response	[27]
Melanoma	PD-1	Blockade with mAbs (pembrolizumab or nivolumab)	19% of treated patient reduced tumor size	[28]
Melanoma	PD-1	Blockade with mAbs (pembrolizumab)	33% of treated patient reduce size tumor	[29]
Rheumatoid arthritis	CD80/CD86	Blockade with soluble receptor (abatacept)	Reduction in the disease index	[30]
Psoriatic arthritis	CD80/CD86	Blockade with soluble receptor (abatacept)	Musculoskeletal clinical improving	[31]
Sjögren syndrome	CD40	Blockade with recombinant antibody (CFZ533 or iscalimab)	Reduction in the disease index	[32]
Kidney graft	CD40	Blockade with recombinant antibody (CFZ533 or iscalimab)	Transplant success rate similar to tacrolimus treatment, but with a lower probability of adverse effects and infections	[33]

CTLA: Cytotoxic T lymphocyte antigen; PD-1: Programmed death-1.

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