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T-CELL INHIBITORS: A BENCH-TO-BEDSIDE REVIEW

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Abstract

Allergic contact dermatitis is the quintessential example of a delayed-in-time and T cell-mediated immune response. In the last decade, many of the molecular events required to initiate (or block) such a response have been uncovered. Textbook and journal reviews have emphasized the co-stimulatory requirements, with less focus on the co-inhibitory signals that are of equal importance in understanding this central event of adaptive immunity. To fill this gap, we offer a compendium of discoveries characterizing the ligand/receptor pairs inhibiting T-cell activation and of selected illnesses and therapeutic applications that illuminate their role in health and disease.

Keywords

T-cell inhibitors; CTLA-4; PD-1; TIM-3; BTLA; SD-4; DC-HIL; allergic contact dermatitis; autoimmune diseases; transplant rejection; cutaneous T-cell lymphoma; melanoma

INTRODUCTION

Adaptive immunity begins when antigen (Ag) is presented by dendritic Ag presenting cells (DC/APC) to naïve T cells that become activated into memory/effector T cells. The immune response is propagated by subsequent similar interactions between DC or other APC (such as B cells and macrophages) with the previously generated and expanding population of memory/effector T cells.

APC regulate T-cell activation via two concomitant signals. The first involves ligation of Ag bound by major histocompatibility complex (MHC) molecules to the T-cell receptor (TCR) on T cells. The second is a composite of positive (co-stimulatory) and negative (co-inhibitory) transductions mediated by binding of APC ligands to other receptors on T cells. The combined effect of the two signals determines whether T cells are activated (to proliferate and secrete cytokines) or inhibited (leading to anergy or apoptotic death) (Figure 1). Most recently, some immunologists have referred to a third signal consisting of cytokines that can even rescue partially activated or even anergic T cells.¹

The predominant co-stimulatory signal results from binding of CD28 on T cells to B7 molecules on APC.^{2,3} By contrast, several pairs of co-inhibitory receptors and ligands have

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been identified (Table 1³⁻⁹, Table 2). Their discovery and relevance to disease states and treatments are the focus of this review.

DISCOVERY AND CHARACTERIZATION OF RECEPTOR/LIGAND PAIRS OF T-CELL INHIBITORS

Over the last two decades, T-cell inhibitor pairs have been identified and characterized including: cytotoxic T lymphocyte antigen-4 (CTLA-4) and B7 molecules CD80/CD86; programmed death-1 (PD-1) and ligands PD-L1 and PD-L2; T-cell immunoglobulin domain and mucin domain 3 (TIM-3) and galectin-9; B- and T-lymphocyte attenuator (BTLA) and herpes virus entry mediator (HVEM); and syndecan-4 (SD-4) and dendritic cell-associated heparan sulfate proteoglycan-integrin ligand (DC-HIL) (Table 1, Table 2). Almost all of these pairs consist of immunoglobulin (Ig) super-family molecules on T cells and B7 family members on APC. The exceptions are HVEM (which belongs to the TNF family) and syndecan-4 and DC-HIL (which are structurally unrelated to the others).

CTLA-4 and B7 Ligands

- CTLA-4 has sequence and structural homology to the co-stimulator molecule CD28.
- CD28 and CTLA-4 bind the same B7 ligands, but the latter does so with higher affinity.
- CTLA-4 deficiency in gene-targeted mice causes a severe and fatal T-cell lymphoproliferative disease.

CTLA-4 was identified through subtractive cloning of a cytotoxic T cell derived cDNA library.¹⁰ Its sequence and structural homology to CD28 and ability to bind B7 led investigators to think it was similar to CD28.^{11,12} However, anti-CTLA-4 Ab increased proliferation of activated T cells, prompting the conclusion that CTLA-4 transmits an inhibitory signal.^{13,14} Moreover, CTLA-4^{-/-} mice developed severe and fatal T-cell lymphoproliferative disease, further supporting the concept of CTLA-4 as a T-cell co-inhibitor.¹⁵ Unlike CD28, which is expressed constitutively, CTLA-4 is expressed only by activated T cells. While both CD28 and CTLA-4 bind B7-1 and B7-2, CTLA-4 has far greater affinity for both B7 molecules.¹² Following CD28-mediated activation of T cells, CTLA-4 subsequently competes with CD28 for B7 as a co-inhibitor of T-cell activation.

PD-1 and PD Ligands (PD-L1 and PD-L2)

- PD-1-deficient mice develop a less severe and more gradual autoimmune phenotype than CTLA-4-deficient mice.
- PD-1 has 2 ligands, PD-L1 and PD-L2.

PD-1 was characterized through subtractive hybridization to search for genes that induce programmed cell death.¹⁶ Like CTLA-4, PD-1 is expressed specifically by activated T cells. However, initially the role of PD-1 in cell death was unclear because it bears structural similarities to both co-stimulators (CD28 and ICOS) and co-inhibitor (CTLA-4). Whereas CTLA-4^{-/-} mice develop severe and fatal T-cell lymphoproliferative disease¹⁵, PD-1^{-/-} mice develop a slow-progressing lupus-like autoimmune phenotype.^{17,18}

Based on homology to other Ig super-family members, the ligand for PD-1 was thought to belong to the B7 family. That ligand, PD-L1 (B7-H1), is co-expressed with B7-1 and B7-2 molecules on APC.¹⁹ PD-L1 inhibits T cell proliferation in wild-type mice but has no

impact on PD-1^{-/-} mice, indicating that PD-L1 inhibits T-cell receptor stimulation.¹⁹ A second ligand, PD-L2 (B7-DC), was also found to antagonize CD28-B7 signaling.²⁰

BTLA and HVEM

- BTLA and HVEM represent the first known interaction between members of the Ig (BTLA) and TNF (HVEM) super-families.
- BTLA-deficient mice are susceptible to autoimmune disease resembling the PD-1 deficient phenotype (but unlike the fatal disease in CTLA-4 deficient mice).

BTLA is another Ig domain-bearing glycoprotein expressed by activated T_H1.²¹ Its ligation to Ag receptors decreased T-cell production of IL-2. Furthermore, T cells lacking BTLA proliferated more avidly, and BTLA^{-/-} mice were more susceptible to experimental autoimmune encephalomyelitis (EAE), an animal model for CNS demyelinating disorders.²¹ That BTLA is the ligand of HVEM was a surprise since this ligand-receptor pairing was the first known interaction of a co-stimulatory TNF family member (HVEM) with an inhibitory Ig super-family receptor (BTLA).^{4,22,23} Our understanding of the BTLA/HVEM pathway is complicated by the finding that HVEM engages not only inhibitory receptors (BTLA, CD160) but also the stimulatory LIGHT receptor.²⁴ CD8⁺T cells hyperproliferate in BTLA- or HVEM-deficient mice. Furthermore, naive cytotoxic T cells from BTLA-deficient mice more efficiently develop memory compared to wild-type cells.²⁵ Thus, with BTLA, there is increasing recognition that negative regulators may serve overlapping functions.

TIM-3 and Galectin-9

- The negative regulatory role of TIM-3 has been studied best in animal models of EAE and autoimmune diabetes.

TIM-3 first came to attention as a surface marker specific for differentiated T_H1 cells but was also found on T_H17 cells.^{7,8} Its role in autoimmunity became apparent when blockade of TIM-3 exacerbated EAE in mice and elevated macrophage levels.²⁶ It also accelerated onset of diabetes in non-obese diabetic mice.²⁷ Using a soluble TIM-3Ig fusion protein, researchers demonstrated CD4⁺CD25⁺ regulatory T cells to express a TIM-3L on their surface after stimulation, whereas the same was not true of CD4⁺CD25⁻ T cells.²⁷ This implicated regulatory T cells as mediators of the inhibitory effect of TIM-3, as was shown for CTLA-4 and PD-1. Further evidence for the inhibitory role of TIM-3 stems from observations that TIM-3Ig administration promotes T_H1 proliferation and cytokine release, with reduced T_H1-mediated tolerance.⁷ Using TIM-3LIg fusion proteins, researchers identified galectin-9 as the TIM-3 ligand.²⁸

DC-HIL and SD-4

- Unlike the protein-protein interactions of Ig super-family members, SD-4 binds to DC-HIL via heparin/heparan sulfate residues.
- An Ig-like PKD extracellular domain mediates the negative function of DC-HIL.

Molecular characterization of DC adhesion during endothelial migration led to isolation of DC-HIL via subtractive cloning methods.²⁹ In addition to heparin-binding and integrin-recognition motifs (RGD) in the extracellular domain, DC-HIL has an Ig-like domain that suggested a role for DC-HIL in cell-cell interactions.^{29,30} Given the constitutive expression of DC-HIL on APC, investigators envisioned DC-HIL to play a role in activating T cells. However, a recombinant form of DC-HIL (DC-HIL-Fc), preferentially bound already activated (but not resting) T cells. Moreover, immobilized DC-HIL-Fc that bound to naïve (and previously activated) T cells caused hypoproliferation, evidenced by decreased IL-2 production and cell-cycle arrest.³⁰ Soluble DC-HIL-Fc, on the other hand, restored T cell

function and promoted T-cell proliferation, most likely by interfering with endogenous DC-HIL binding to its ligand on T cells.³⁰ Specifically, the Ig-like PKD was critical for DC-HIL's inhibitory function, as PKD-deficient mutant DC-HIL-Fc molecules were unable to elicit T-cell proliferation in response to anti-CD3.³⁰ Thus DC-HIL is a T-cell inhibitor, and a search for its ligand revealed the heparan sulfate-proteoglycan, syndecan-4 (SD-4).⁶ Blocking SD-4 caused decreased binding of DC-HIL to T cells. Knocking down SD-4 led to increased T-cell proliferation. This confirmed SD-4 to be the ligand responsible for the co-inhibitory function of DC-HIL.⁶ These findings have been supported further by studies in human allogeneic APC/T-cell interactions.³¹

T-CELL INHIBITORS IN DISEASE AND THERAPEUTICS

The following discussion is categorized into conditions of: (1) deficient T-cell inhibition resulting in overactive T cells (causing autoimmune diseases, allergic contact dermatitis, and organ transplant rejection) and (2) excessive T-cell inhibition resulting in underactive T cells (causing cancers).

DEFICIENT T-CELL INHIBITION RESULTING IN T-CELL OVERACTIVITY

Autoimmune diseases

- T-cell inhibitors prevent autoimmunity by dampening autoreactive T-cell proliferation directly or indirectly via regulatory T cells (Tregs).
- T-cell inhibitor polymorphisms have been identified in patients with such autoimmune diseases as Graves', autoimmune hypothyroidism, type 1 diabetes, systemic lupus erythematosus, and rheumatoid arthritis.
- Animal models for systemic lupus erythematosus (SLE), experimental autoimmune encephalomyelitis (EAE), autoimmune diabetes mellitus (ADM), rheumatoid arthritis (RA), and psoriasis have confirmed a role for T-cell inhibitors in these diseases.
- Humanized CTLA-4Ig (Abatacept; Orencia) was approved by the FDA for treating RA and is undergoing clinical trials for other autoimmune conditions.

Autoimmunity develops when immune responses fail to maintain self-tolerance. CD4⁺CD25⁺FOXP3⁺Tregs constitutively express CTLA-4, which down-regulates B7-1 and B7-2 on DC,³² and these cells prevent autoimmunity by curtailing maturation of naïve T cells³³ and DC.³⁴ BTLA^{-/-} mice develop autoimmune hepatitis, sialadenitis, and pulmonary disease.³⁵ TIM-3-deficient mice or mice treated with full-length and soluble TIM-3 Ig develop hyper-proliferative T-cells with elevated IL-2 secretion.⁷

Human CTLA-4 polymorphisms are associated with Graves' disease, autoimmune hypothyroidism, and type 1 diabetes.³⁶ SLE patients have dysfunctional CTLA-4 on FOXP3⁺ T cells³⁷ and reduced expression of CD4⁺CD25⁺ Tregs.³⁸ Sjogren syndrome patients have elevated PD-1 in salivary T cells.³⁹ Polymorphisms in the PD-1 gene have also been identified in SLE, type 1 diabetes, MS, and RA.⁴⁰⁻⁴³ PD-1 deficient mice can develop an SLE-like phenotype and fatal autoimmune cardiomyopathy.^{5,17,44} TIM-3/TIM-3L may also play a role in SLE pathogenesis via Tregs.⁴⁵

BTLA^{-/-} mice develop severe forms of EAE, the animal model for CNS demyelinating disorders, such as, multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM)²¹ and blocking TIM-3 function hastens demyelination seen in EAE.²⁶ Anti-human TIM-3 Ab blocked TIM-3 function of CD4⁺T cells from MS patients. Glatiramer and IFN-β

(traditional treatments for MS) restored the ability of T cells from MS patients to up-regulate IFN- γ in response to TIM-3 blockade.⁴⁶

Non-obese diabetic (NOD) mice are the animal model for autoimmune diabetes mellitus (ADM), which can be precipitated by blocking PD-1 and PD-L1.⁴⁷ TIM-3 inhibition also precipitated ADM, abrogating tolerance in an islet allograft model treated with donor-specific transfusion and CD40L.²⁷ Anti-BTLA Ab eliminated BTLA⁺ B cells and CD4⁺ T_H cells; elevated IL-4, IL-10, IFN- γ and IL-2 production; and enhanced proliferation of Tregs in ADM.⁴⁸ Anti-BTLA Ab forestalled disease onset, whereas anti-PD-1Ab enhanced disease progression.⁴⁸ Co-administration of anti-BTLA and anti-PD-1 Ab delayed ADM onset and was associated with reduced pancreatic islet infiltration of B and CD4⁺ T cells while increasing Tregs.⁴⁸

In RA, hyperproliferative synoviocytes lead to pannus formation and the bone destruction that characterizes this autoimmune condition. Galectin-9 seems to be up-regulated in synovial tissue and fluid of RA patients (vs osteoarthritis patients).⁴⁹ Fibroblast-like synoviocytes from RA patients were more susceptible to apoptosis when exposed to proteolysis-resistant mutant galectin-9 (vs. wild-type galectin-9).⁴⁹ In collagen-induced arthritis (CIA – a mouse model for RA), galectin-9 treatment prevented and, in fact, improved CIA.⁵⁰ Galectin-9 promoted Treg expression and inhibited T_H17 cells (and therefore IL-17) in inflamed joints of CIA mice. Galectin-9-deficient mice more readily acquired CIA with lower levels of splenic Tregs.⁵⁰ Thus it seems that galectin-9 promotes synoviocyte apoptosis and thereby suppresses RA progression.

In psoriasis, reduced activity of CD25^{high}CTLA-4⁺Foxp3^{high} Tregs is thought to inadequately suppress effector T cells.⁵¹ Galectin-9 limited epidermal thickness and decreased production of IL-17 and IL-22 in an IL-23-induced psoriasis mouse model.⁵²

The higher binding potential of CTLA-4 to B7 molecules¹² has made it a target for dampening co-stimulatory signals in autoimmune diseases. The CTLA-4Ig fusion protein Abatacept (Orencia) has been used to treat RA. In addition, it is undergoing trials for treatment of moderate-to-severe ulcerative colitis (clinicaltrials.gov NCT00410410), new-onset type 1 diabetes (clinicaltrials.gov NCT00505375), and MS.⁵³ The combination of Abatacept and cyclophosphamide is being tested for lupus nephritis (ACCESS trial, clinicaltrials.gov NCT00774852).

Allergic contact dermatitis (ACD)

- ACD can be prevented by blocking co-stimulatory signals (e.g. using anti-CTLA-4Ab) or by enhancing co-inhibitory signals (e.g. using galectin-9 mutants or toxin-conjugated DC-HIL).
- Conversely, ACD is augmented by inhibiting negative signals (e.g. using anti-CTLA-4 Ab or using soluble DC-HIL to block SD-4).

ACD to the hapten 2,4-dinitrofluorobenzene (DNFB) in mice was attenuated by infusion of CTLA-4Ig,⁵⁴ whereas ultraviolet B-induced tolerance to the same hapten was broken by CTLA-4 blockade.⁵⁵ A stable mutant of galectin-9suppressed ACD in mice manifested by reduced ear swelling with fewer IFN- γ and IL-17-producing T cells in draining lymph nodes.⁵²

Infusion of soluble DC-HIL (which prevents binding of DC-HIL to its ligand SD-4 on T cells) during challenge (but not sensitization) produced more robust ACD.³⁰ This indicates that soluble DC-HIL competes with endogenous DC-HIL for ligation of SD-4 on T cells and thus counteracts its negative signal. In addition, blocking SD-4 through anti-SD-4 Ab or

soluble SD-4 receptor also augmented ACD and caused hyper-proliferation of T cells in mixed lymphocyte reactions.⁶

Only a subset of activated T cells express SD-4 (the exclusive ligand of DC-HIL), making it a potentially useful target for therapeutic intervention. DC-HIL conjugated to a ribosome inactivating protein, saporin toxin, led to elimination of SD-4⁺ activated T cells *in vitro*.⁵⁶ By extension, hapten-sensitized mice infused with saporin-bearing DC-HIL before (but not during) hapten challenge experienced markedly less-severe ACD.⁵⁶ Such mice have fewer SD-4⁺ effector memory T cells in both haptenated skin and draining lymph nodes in addition to lower levels of IFN- γ , IL-10, and IL-17.⁵⁶

Transplant Rejection

- T-cell inhibitor levels are increased in mismatched allografts.
- Blocking negative regulators can accelerate transplant rejection.
- Belatacept (Nulojix, another CTLA-4Ig) was equivalent to cyclosporine as an immunosuppressant in renal transplantation.

Because allograft rejection is T-cell mediated, identification of T-cell inhibitory mechanisms to curtail such catastrophic responses can be beneficial.

BTLA, but not PD-1, mRNA is up-regulated in partially MHC-mismatched cardiac allografts and associated with longer survival.⁵⁷ However, other studies have demonstrated that allograft rejection leads to elevated PD-1 and PD-L levels.^{58,59} Conversely, allograft rejection was caused by blockade of the BTLA/HVEM pathway and in BTLA^{-/-} mice.⁵⁷ Regardless of BTLA and PD-1 expression, fully mismatched allografts were rapidly rejected.⁵⁷ In such allografts, PD-1 blockade accelerates rejection, whereas BTLA blockade, surprisingly, enhances PD-1 expression of alloreactive T cells and prolongs graft survival.⁵⁷ At low levels of *in vitro* T-cell activation, BTLA was the main negative regulator expressed. On the other hand, increasing levels of T-cell activation correlated with higher levels of PD-1 expression.⁵⁷ These studies demonstrated BTLA to have the dominant role in partial MHC-mismatching. PD-L1Ab treatment of CD28^{-/-} recipients increased allograft survival⁶⁰ mediated by lowered levels of IFN- γ and IFN- γ -induced chemokines.⁵⁸

In a mouse model of graft-versus-host disease, TIM-3 was more highly expressed in hepatic and splenic T cells, DC, and macrophages.⁶¹ Blocking TIM-3 accelerated GVHD.⁶¹ Since CD8⁺ T cells drive acute allograft rejection and TIM-3 induces apoptosis in T_H1 cells, investigators wondered what role TIM-3 may play in rejection. Galectin-9 promoted apoptosis of CD8⁺ T cells *in vitro* and enhanced skin graft survival *in vivo*.⁶² These observations have been extended to fully allogeneic skin grafts⁶³ and solid organ transplant rejection. Galectin-9 enhanced graft survival and reduced CD4⁺ and CD8⁺ T-cell infiltration in a mouse cardiac allograft model.⁶⁴ In allograft nephrectomy samples from patients suffering acute rejection, TIM-3 and galectin-9 mRNA expression patterns correlated with severity of rejection.⁶⁵ A number of animal allograft rejection models have demonstrated potential benefits for anti-CTLA-4Ab, paving the way for clinical trials.^{66–68} Belatacept (Nulojix) is a CTLA-4fusion protein that differs from Abatacept by two amino acids; it is equivalent in immunosuppressive efficacy to cyclosporine 6 months after renal transplantation from living donors.⁶⁹

EXCESSIVE T-CELL INHIBITION RESULTING IN UNDERACTIVE T CELLS

Whereas hyper-autoreactive immune responses may cause autoimmunity, ACD, or transplant rejection, an abnormally suppressed immune system allows cancers to proliferate unchecked. Tumor evasion of host immune responses can be mediated by two separate

mechanisms: (1) enhanced expression of T-cell inhibitors by cancer cells, which down-regulates tumor-specific T-cell activation; or (2) recruitment of Tregs to inhibit naïve T cells from maintaining systemic tolerance and thus interfere with the anti-tumor role of specific T cells.⁷⁰ Tregs proliferate at tumor sites, where they inhibit T cell-mediated cytotoxicity. Elimination of CD4⁺CD25⁺Tregs elicits tumor-sensitive CD8⁺ T cells to eliminate syngeneic tumors in mouse models. This is supported by findings in acute myelogenous leukemia patients, who over-express Tregs.⁷¹

Cutaneous T-cell lymphoma (CTCL)

- Cutaneous T-cell lymphoma is associated with up-regulated expression of CTLA-4 and SD-4.
- T cells from patients with CTCL are lysed by toxin-conjugated DC-HIL.

Dysregulation and hyper-proliferation of T cells underlies CTCL pathophysiology. CTCL cells have been shown to evade the immune system by acquiring CD4⁺CD25⁺FOXP3⁺Treg phenotype and up-regulating CTLA-4 expression.⁷² SD-4 is robustly expressed and susceptible to saporin-bearing DC-HIL.⁵⁶ Most recently, Chung *et al.* have examined SD-4 expression in the leukemic variant of CTCL, Sezary syndrome (SS). In peripheral blood mononuclear cells (PBMCs) isolated from blood samples of patients with SS, SD-4 is constitutively over-expressed by the malignant memory T cells. This was not seen in T cells isolated from patients with atopic dermatitis, psoriasis, mycosis fungoides, or healthy donors. They further demonstrated that over-expressed SD-4 was responsible for inhibiting T-cell activation following ligation to DC-HIL and showed saporin toxin-bound DC-HIL to prevent proliferation of CTCL cells.⁷³

Melanoma

- Anti-CTLA-4 Ab (ipilimumab; Yervoy) has been approved by the FDA for treatment of metastatic melanoma.
- Melanoma is associated with up-regulated expression of DC-HIL and TIM-3. When implanted into immunocompetent mice, melanoma knocked-down for DC-HIL expression grows less markedly compared to wild-type melanoma.
- Anti-PD1 Ab has been well-tolerated by patients with metastatic cancers, including melanoma.

Most recently, the anti-CTLA-4 Ab (ipilimumab; Yervoy) was approved by the FDA for treatment of metastatic melanoma. Patients with unresectable stage III or IV melanoma, who had failed treatment with one or more standard chemotherapies, were randomized to ipilimumab alone, gp100 peptide vaccine alone, or combination ipilimumab/gp100. Patients who received ipilimumab (with or without gp100) survived approximately 10 months, compared to 6.4-month survival in those who were given only the gp100 peptide vaccine.⁷⁴ However, not surprisingly, a major limitation of ipilimumab treatment has been autoimmune conditions producing dermatitis, hepatitis, and colitis, similar to findings in CTLA-4 knock-out mice.⁷⁴

Melanoma constitutively expresses high levels of DC-HIL, which may reflect the ability of this cancer to evade adaptive immunity, since DC-HIL inhibits T-cell activation. Investigators tested this hypothesis by generating mouse melanoma cells with knocked-down DC-HIL. While retaining normal phenotype (cell morphology and growth, melanin synthesis, and MHC class I expression), these melanoma cells proliferate at a markedly reduced rate after subcutaneous implantation into immunocompetent mice.⁷⁵ The attenuated tumor growth was attributed to greater proliferation of melanoma-specific T cells due to reduced DC-HIL expression. These findings indicate that melanoma can circumvent the

immune system through DC-HIL-mediated inhibition of tumor-selective T cells and that the DC-HIL/SD-4 pathway is a promising therapeutic target for this malignancy.

Tumor cells evade host immune surveillance by up-regulating PD-L1 (B7-H1), thereby offering yet another target for cancer immunomodulation through blockade of either PD-1 or its ligands.^{76,77} Single-agent therapy with the anti-PD1 Ab has been well-tolerated in Phase 1 trials of patients with advanced metastatic solid and hematologic cancers, including melanoma.⁷⁸ Given that CTLA-4 and PD-1 are both negative regulators of T-cell function, studies are in progress to assess the efficacy of dual-blockade. In a mouse melanoma model, blockade of CTLA-4 alone led to elimination of 10% of pre-implanted tumors. Targeting of both CTLA-4 and PD-1 resulted in 65% rejection of pre-implanted tumors with increased effector T cells and cytokine production.⁷⁹

CONCLUSION

T-cell inhibitors help orchestrate the complexities of adaptive immunity. Dysregulation can lead to: increased T-cell activity, producing autoimmunity, hypersensitivity, and transplant rejection; or reduced tumor-specific T-cell activity producing malignant cell proliferation. Several T-cell inhibitor pairs are being investigated in animal models and clinical trials of T cell-driven diseases (Table 3). Two T-cell inhibitor-based immunomodulators, abatacept (Orencia) and ipilimumab (Yervoy) were FDA-approved for rheumatoid arthritis and metastatic melanoma, respectively. Studies of T-cell inhibitors in ACD, melanoma, psoriasis, and CTCL should soon produce targeted treatment of dermatologic disorders.

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A. T-cell activation **B. T-cell anergy**

Figure 1.
apc regulation of T-cell activation

Table 1

Pairs of co-inhibitory ligands and receptors expressed by T cells and antigen presenting cells (APC), respectively

Expression	T cell surface receptor	APC ligand	Expression
T(inducible)	CTLA-4	B7-1 B7-2	T, B, DC, monocytes
T, B(inducible)	PD-1	PD-L1(B7-H1)	Resting:T, B, monocytes, DC
		PD-L2(B7-DC)	Monocytes, DC (inducible)
T _H 1, T _H 17, T _{reg} , CD8 ⁺ , DC, monocytes	TIM-3	Galectin-9	T _H 1
T _H 1, B, DC	BTLA	HVEM	T, B, NK, DC, myeloid
T, B(constitutive), endothelial cells	SD-4	DC-HIL	DC, LC, macrophages

Adapted from Carreno³, Murphy⁴, Okazaki⁵, Chung⁶, Sabatos⁷, Hastings⁸, Anderson⁹; B =B cells, DC =dendritic cells, LC =Langerhans cells, NK=natural killer cells, T=Tcells, T_H=T helper cells

Table 2

CD designations (in parentheses) for co-stimulatory and co-inhibitory molecules.

Co-stimulatory molecules:	
<u>T cell surface receptor</u>	<u>APC ligand</u>
CD40-L (CD154)	CD40
ICOS (CD278)	ICOS-L(CD275)
CD28	B7-1 (CD80) B7-2 (CD86)
LFA-1 (CD18/CD11a)	ICAM-1 (CD54)
Co-inhibitory molecules:	
<u>T cell surface receptor</u>	<u>APC ligand</u>
CTLA-4 (CD152)	B7-1 (CD80) B7-2 (CD86)
PD-1 (CD279)	PD-L1 (CD274) PD-L2 (CD273)
TIM-3	Galectin-9
BTLA (CD 272)	HVEM
SD-4	DC-HIL

Table 3

Conditions in which co-inhibitory molecules have been implicated

	Illuminate Pathogenesis	Therapy
Allergic contact dermatitis	CTLA-4, Galectin-9, SD-4	
Autoimmune hypothyroidism	CTLA-4	
Cutaneous T-cell lymphoma	CTLA-4, SD-4	
Experimental autoimmune encephalomyelitis (EAE)	BTLA, TIM-3	CTLA-4 Ig (abatacept)
Graves' disease	CTLA-4	
Melanoma	DC-HIL, TIM-3, PD-L1	Anti-CTLA-4 (ipilimumab)
Psoriasis	CTLA-4, Galectin-9	CTLA-4 Ig (abatacept)
Rheumatoid arthritis	Galectin-9	CTLA-4 Ig (abatacept)
Sjogren's	PD-1	
Systemic lupus erythematosus	CTLA-4, PD-1, TIM-3	
Transplant rejection	BTLA, PD-1, TIM-3	CTLA-4 Ig (belatacept)
Type 1 (autoimmune) DM	CTLA-4, PD-1, BTLA	CTLA-4 Ig (abatacept)
Ulcerative colitis		CTLA-4 Ig (abatacept)