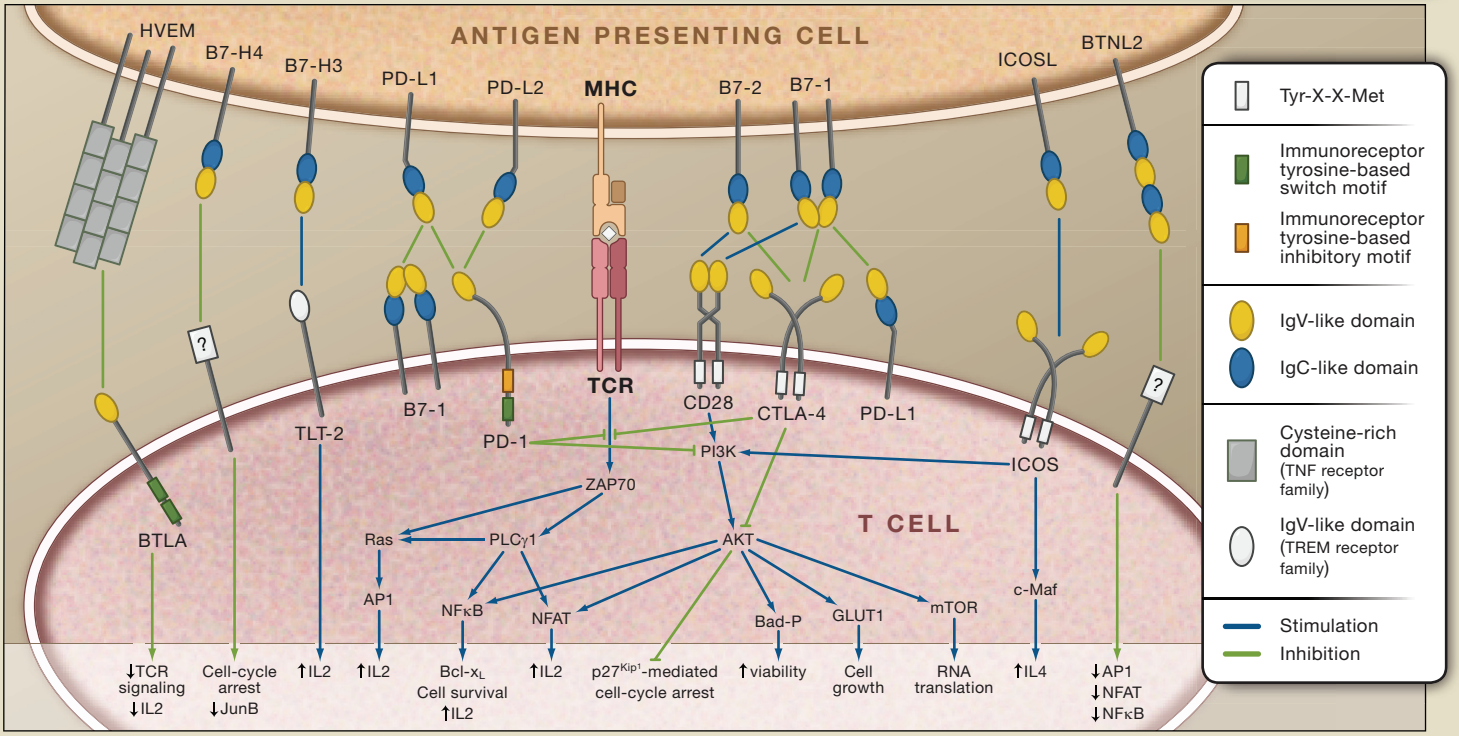
SnapShot: B7/CD28 Costimulation

Alison M. Paterson, Vijay K. Vanguri, and Arlene H. Sharpe
Department of Pathology, Harvard Medical School, Boston, MA 02115, USA

Cell

Ligand	Ligand Expression	Receptor/Expression	Function of Receptor on T Cells	Implications for Human Disease
B7-1 (CD80)	Inducible: APCs (slower kinetics than B7-2), T cells	CD28 Constitutive: mouse (all T cells), human (95% of CD4+, 50% of CD8+ T cells), plasma cells, NK cells	Stimulation of naive and previously activated T cells upon TCR ligation: ↑ proliferation (↓ $p27^{Kip1}$, ↑ G_1/S); ↑ cytokine production (↑ NFκB, ↑ IL2); ↑ survival (↑ Bcl-x_L, ↑ survival of Tregs); ↑ glucose metabolism; provides T cell-dependent B cell help for class switching.	Blockade of pathway to treat autoimmune inflammatory diseases and for transplantation; active engagement to expand anti-tumor T cells and Tregs
B7-2 (CD86)	Constitutive at low levels; inducible: APCs, T cells			
B7-1	Inducible: APCs (slower kinetics than B7-2), T cells	CTLA-4 (CD152) Inducible: T cells; constitutive: Tregs	Inhibition of TCR-dependent activation: ↓ proliferation (↑ $p27^{Kip1}$, ↓ G_1/S); ↓ cytokine production (↓ NFκB, ↓ IL2); CD28-dependent and -independent functions; promotes inhibitory function of Tregs.	Blockade of pathway in tumor immunotherapy; receptor polymorphisms linked with autoimmunity
B7-2	Constitutive at low levels; inducible: APCs, T cells			
ICOSL (B7h, B7-H2, CD275, LICOS, B7RP-1)	Induced by TNFα and IFNγ: APCs, T cells, fibroblasts, endothelium	ICOS (CD278) Inducible: T cells (CD28-dependent and CD28-independent); constitutive: resting memory T cells, Tregs	Stimulation: ↑ proliferation (modest compared to CD28); ↑ cytokine production by effector T cells (IL4 > IFNγ); ↑ survival (↑ Bcl-x_L, ↑ IL23-mediated survival of Th17); ↑ GC formation and isotype class switching. Inhibition: ↑ IL10 cytokine production.	Receptor polymorphisms associated with immunodeficiency and autoimmunity
PD-L1 (B7-H1, CD274)	Constitutive (mouse), induced by IFNα/β/γ: APCs, T cells, nonhematopoieitic cells; overexpressed in tumor cells	PD-1 (CD279) Inducible: T cells, double-negative thymocytes, B cells, myeloid cells; constitutive: exhausted T cells during chronic viral infection	Inhibition: ↓ TCR signals through recruitment of protein tyrosine phosphatases (most effective at low levels of TCR signaling); ↓ cytokine production (↓ IL2, IFNγ, TNFα); ↓ proliferation (↓ G_1/S); ↓ cytokine production greater than ↓ proliferation; ↓ survival (↓ Bcl-x_L); ↓ CTL-mediated lysis.	Active engagement induces tolerance; ↑ PD-L1 on human tumors associated with poor prognosis (potential for blockade as therapy); ↑ PD-1 on T cells associated with poorer function in chronic viral infection (potential for blockade as therapy)
PD-L2 (B7-DC, CD273)	Inducible: DCs, macrophages, placenta (human); over-expressed in tumor cells			
B7-1	see above	PD-L1 (B7-H1; CD274)	Inhibition of T cell proliferation	see above
PD-L1	see above	B7-1 (CD80)	Inhibition of T cell proliferation	see above
B7-H3 (CD276)	Inducible: T cells, B cells, DCs, NK cells; overexpressed in tumor cells	TLT-2 (TREM receptor family; mouse only) Constitutive: CD8+ T cells, B cells, macrophages, DCs; inducible: CD4+ T cells	Stimulation of CD8+ T cells: ↑ proliferation; ↑ cytokine production (↑ IFNγ and IL2); blockade leads to ↓ contact hypersensitivity in vivo.	Costimulatory effect of B7-H3 may regulate antitumor cytotoxic T cell immune responses
B7-H4 (B7S1, B7x)	Inducible: T cells, B cells, DCs, monocytes; overexpressed in tumor cells	Receptor not yet identified Putatively inducible on T cells	Inhibition of T cell proliferation: ↓ cytokine production (↓ IL2 and IL4); blockade/knockdown leads to ↑ EAE and tumor cell apoptosis.	Potential role in tumor immunotherapy
BTNL2 (BTL-II)	Inducible: T cells, B cells	Receptor not yet identified Putatively inducible on T cells	Inhibition of CD4+ T cell function in vitro: ↓ proliferation of CD4+ T cells; ↓ ICOSL-mediated cytokine production (↓ TNFα, IFNγ, IL2, IL4, IL6, IL10, and IL17); ↓ activity of AP1, NFAT, and NFκB.	Polymorphisms/mutations in *BTNL2* gene associated with sarcoidosis and inclusion body myositis
HVEM (TNFR superfamily member)	Constitutive, ↓ upon activation: naive T cells, naive B cells, immature DCs, memory T and B cells, nonhematopoietic cells	BTLA (CD272) Inducible: T cells (↑ on anergic T cells), DCs; constitutive: B cells CD160, LIGHT	Inhibition of CD4+ T cell proliferation: ↓ cytokine production (↓ IL2); deficiency promotes EAE and allograft rejection in vivo; BTLA-deficient mice develop autoimmune-like disease.	Pathway blockade enhances immune responses; one polymorphism associated with ↑ risk of rheumatoid arthritis

Stimulatory interaction	Inhibitory interaction	Stimulatory and inhibitory interaction



See online version for legend and references.

SnapShot: B7/CD28 Costimulation

Alison M. Paterson, Vijay K. Vanguri, and Arlene H. Sharpe
Department of Pathology, Harvard Medical School, Boston, MA 02115, USA

Cell

Table: Binding Partners in the B7/CD28 Family of Costimulatory Molecules

T cells require two signals for optimal activation. The first signal is delivered to the T cell receptor (TCR) by processed antigen displayed by major histocompatibility complex (MHC) molecules; this antigen-dependent signal provides specificity to the immune response. The second signal, known as the costimulatory signal, is delivered to receptors on T cells by costimulatory molecules. These cell-surface molecules provide contextual information that influences the ensuing immune response. Costimulatory signals can have either stimulatory or inhibitory effects on T cells. As several interactions can occur throughout the activation and effector phases of the immune response, it appears that the overall balance between positive and negative costimulation directs the magnitude, location and type of response. Temporal and spatial regulation of expression of both costimulatory receptors and ligands leads to dynamic modulation of T cell priming, homing, and effector function. Importantly, these molecules potentially can be targeted for therapy to block undesirable immune activation, for example during autoimmune disease or organ transplant rejection, or to stimulate desired immune responses to combat cancer or infection. The best described costimulatory interactions are those in the B7/CD28 family. B7 family members typically act as ligands for CD28 receptor family members, although B7-1 and PD-L1 (both B7 family members) can also act as receptors themselves. There are also crossfamily interactions, such as B7-H3 binding to the TREM receptor family member TREM-like transcript-2 (TLT-2) and BTLA binding to HVEM . HVEM also binds to LIGHT (TNF superfamily, member 14) and to lymphotoxin α to stimulate T cell responses; HVEM can also bind to CD160, an Ig superfamily member, to inhibit T cell responses. Other members of the B7/CD28 family may still await discovery, and alternative receptors for known family members may exist. For example, there are data to suggest the existence of a stimulatory receptor for PD-L1 and PD-L2. B7-H3 may also interact with a putative inhibitory receptor on T cells in addition to the stimulatory TLT-2.

Figure: B7/CD28 Family Interactions and Signaling Pathways

B7/CD28 family members are defined structurally by their common IgC-IgV extracellular binding domains, and signaling pathways are driven primarily by intracellular tyrosine-containing motifs. Apart from the specific antigen-dependent signal provided by the MHC-antigen complex to the TCR, the cell-surface interactions involving the B7/CD28 family of costimulatory molecules provide a second signal to T cells to enhance or inhibit the canonical TCR signaling pathway, leading to changes in T cell proliferation, survival, and cytokine production. Human B7-H3 has an extracellular domain composed of IgV-IgC-IgV-IgC, whereas the mouse form of B7-H3 (shown in the figure) consists of an IgV-IgC extracellular domain.

Abbreviations

AP1, activator protein 1; APCs, antigen-presenting cells; B7-H, B7 homolog; BTLA, B and T lymphocyte attenuator; BTNL2, butyrophilin-like 2; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T lymphocyte antigen-4; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; GC, germinal center; GVHD, graft-versus-host disease; HVEM, herpesvirus entry mediator; ICOS, inducible costimulator; ICOSL, ICOS ligand; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LIGHT, homologous to lymphotoxins, exhibits inducible expression, and competes with herpes simplex virus glycoprotein D for HVEM, a receptor expressed by T lymphocytes; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor kappa B; NK, natural killer; PD-1, programmed death-1; PD-L, programmed death-1 ligand; PI3K, phosphatidylinositol 3 kinase; PLC, phospholipase C; Th17, IL17-producing helper T cell; TNF, tumor necrosis factor; TNFR, TNF receptor; Tregs, regulatory T cells; TREM, triggering receptor expressed on myeloid cells; ZAP70, zeta-associated protein kinase 70.

ACKNOWLEDGMENTS

The first two authors contributed equally to this work.

REFERENCES

Alegre, M.L., Frauwirth, K.A., and Thompson, C.B. (2001). T-cell regulation by CD28 and CTLA-4. Nat. Rev. Immunol. *1*, 220–228.

Bluestone, J.A., St Clair, E.W., and Turka, L.A. (2006). CTLA4Ig: Bridging the basic immunology with clinical application. Immunity *24*, 233–238.

Freeman, G.J. (2008). Structures of PD-1 with its ligands: sideways and dancing cheek to cheek. Proc. Natl. Acad. Sci. USA *105*, 10275–10276.

Keir, M.E., Butte, M.J., Freeman, G.J., and Sharpe, A.H. (2008). PD-1 and its ligands in tolerance and immunity. Annu. Rev. Immunol. *26*, 677–704.

Kroczek, R.A., Mages, H.W., and Hutloff, A. (2004). Emerging paradigms of T-cell co-stimulation. Curr. Opin. Immunol. *16*, 321–327.

Murphy, K.M., Nelson, C.A., and Sedy, J.R. (2006). Balancing co-stimulation and inhibition with BTLA and HVEM. Nat. Rev. Immunol. *6*, 671–681.

Okazaki, T., and Honjo, T. (2006). The PD-1-PD-L pathway in immunological tolerance. Trends Immunol. *27*, 195–201.

Salomon, B., and Bluestone, J.A. (2001). Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. Annu. Rev. Immunol. *19*, 225–252.

Zang, X., and Allison, J.P. (2007). The B7 family and cancer therapy: costimulation and coinhibition. Clin. Cancer Res. *13*, 5271–5279.

Zou, W., and Chen, L. (2008). Inhibitory B7-family molecules in the tumour microenvironment. Nat. Rev. Immunol. *8*, 467–477.

  DOI 10.1016/j.cell.2009.05.015