

Costimulation and B7 Family

Overview

T cell activation is a tightly regulated event involving complex receptor-ligand interactions, ultimately leading to downstream signaling events. Optimal activation of naive T cells requires at least two signals, antigen recognition and costimulation. The TCR complex, which recognizes antigenic peptides presented by MHC molecules, is critical in maintaining the specificity of the immune response. Signal two, or costimulation, is an antigen-independent signal required for sustained cell proliferation, effector/memory cell generation and prevention of anergy or apoptosis. Since costimulatory molecules are required for the activation of naive T cells their expression is limited to professional antigen presenting cells (APCs). This ensures that only pathogen-specific T cells are activated and minimizes the chances of acquired immune responses being mounted against self.

Numerous costimulatory molecules have been identified playing a role in the initiation of immune responses by T and B lymphocytes. One of the most well studied costimulatory pathways involves the interaction of B7.1 (CD80) and B7.2 (CD86) with their ligand CD28 on naive T cells. Signals provided through CD28-B7 interactions are essential for initial naive T cell activation leading to increased IL-2 production and IL-2R α (CD25) expression. CD28-B7 interactions can be substituted by NKG2D on naive CD8+ T cells. NKG2D binds to the MHC-related proteins MIC and Rae-1 and induces IL-2 production and proliferation. In other cell types, such as B cells, activation requires CD40-CD40L interactions for proper antibody response. CD40L on activated CD4+ T cells binds to CD40 on B cells promoting survival, cytokine receptor expression, and inducing antibody class switch. In addition to the costimulatory pathways that are important in naive lymphocyte activation, other costimulatory molecules play a role in effector/memory lymphocyte activation.

The costimulatory receptors ICOS, OX-40, 4-1BB, and CD27 bind to their ligands B7h, OX-40L, 4-1BBL, and CD70, respectively. These interactions enhance the activation, survival, and cytokine secretion of effector/memory, but not naive T and B cells. ICOS affects all aspects of acquired immune responses while CD27 affects only T cell responses. OX-40 and 4-1BB are thought to be more specific, with OX-40 generally affecting CD4+ T cells and 4-1BB usually affecting CD8+ T cells. The pattern of expression of these costimulatory receptors and their ligands differs from CD28-B7 in that they are not constitutively expressed but are induced on differentiated T cells, and their ligands are not restricted to APCs.

T cell activation generally incorporates a self-limiting mechanism, such as inhibitory costimulators, to regulate T cell tolerance and attenuate the immune response. The expanding set of inhibitory costimulators currently includes CTLA-4 (CD152), PD-1, and BTLA. While expression of these molecules is induced following T cell activation, they are absent on naive T cells. CTLA-4 binds the same ligands as CD28 but with much higher affinity and subsequently terminates T cell activation. The ligands for PD-1 and BTLA, PD-L1/PD-L2, and B7x, respectively, are expressed on immune cells as well as non-hematopoietic cells. Triggering of PD-1 or BTLA inhibits T cell proliferation and cytokine production. Lastly, B7-H3 is a new costimulatory ligand originally described to induce T cell proliferation and IFN- γ production through an as of yet unidentified receptor. The recent generation of B7-H3-deficient mice, however, suggests that it is an inhibitory costimulator.

As positive costimulation can enhance T and B cell activation, inhibitory costimulation can just as strongly attenuate these responses. The final outcome of an immune response likely depends on the balance between these positive and negative signals.

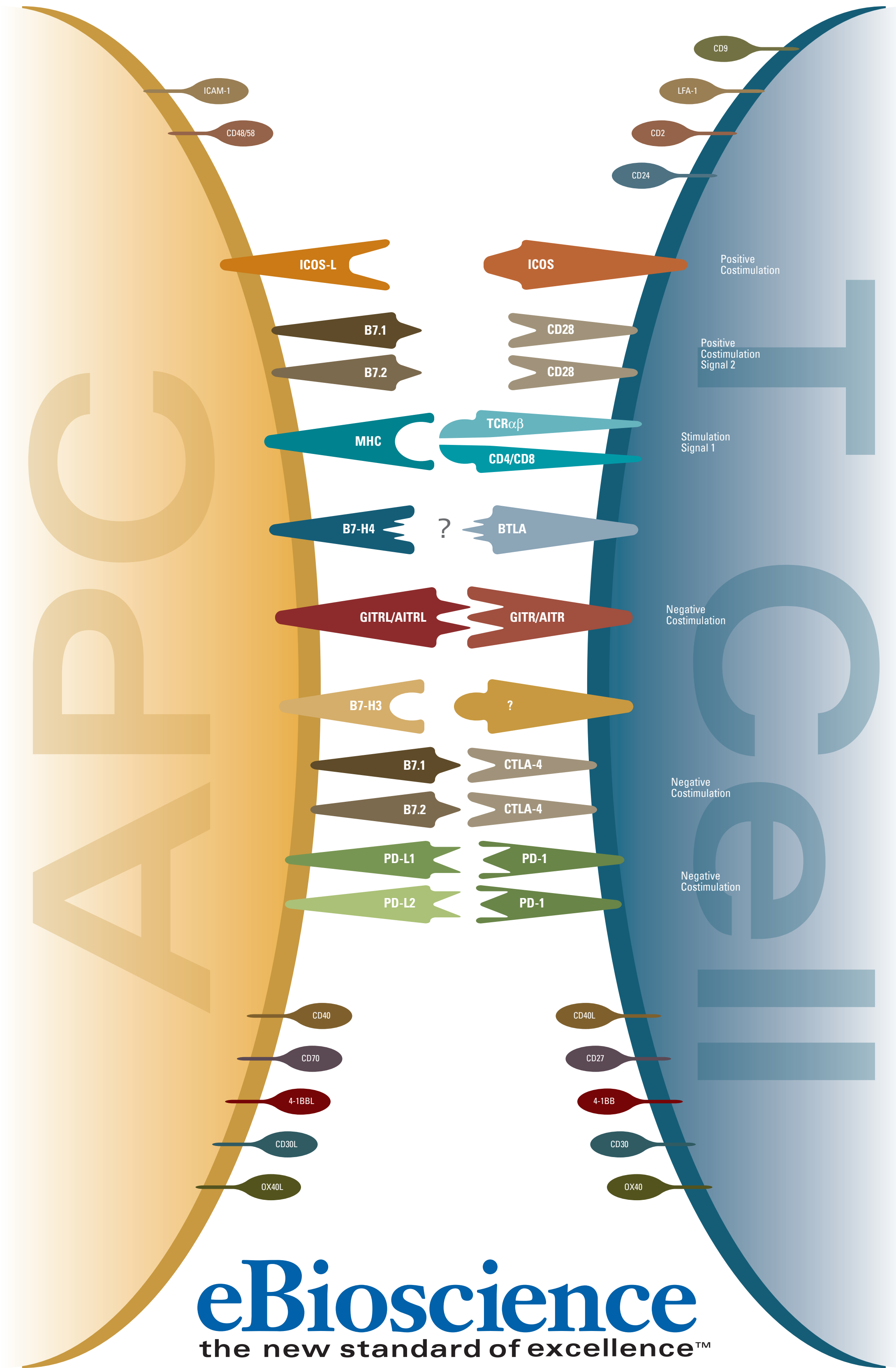
Receptor: CD28 Family	Other Names	Function	Expression	Ligand: B7 Family	Other Names	Expression
CD28	T44	Costimulation	T and NK cells	B7.1	CD80	Activated APC
				B7.2	CD86	APC (upregulated) activated T cells
CTLA-4	CD152	Inhibition	Activated T cells	B7.1	CD80	Activated APC
				B7.2	CD86	APC (upregulated) activated T cells
ICOS	H4, CRP-1, AILIM	Costimulation	Activated T cells	B7RP-1	ICOSL, GL50, B7-H2, B7h	APC
?				B7-H3		

Inhibitory Molecules	Other Names	Function	Expression	Ligand: B7 Family	Other Names	Expression
PD-1		Inhibition	Activated T and B cells	PD-L1	B7-H1	Leukocytes
				PD-L2	B7-DC	Monocytes, macrophages, DC
?				B7.1	CD80	Activated APC
				B7.2	CD86	APC (upregulated) activated T cells

TNFR Family	Other Names	Function	Expression	Ligand: TNF Family	Other Names	Expression
CD27	T14	Costimulation	T cells, B subset, NK	CD70		Activated B cells
CD30	Ki-1	Costimulation, apoptosis	Activated T, NK and B cells	CD153	CD30L	Neutrophils, activated B and T cells
CD40L	CD154, gp39, TRAP	Activation	Activated T cells	CD40		APC, T subset, endothelium, cardiac myocytes, fibroblasts
4-1BB	CD137	Costimulation	Activated T cells	4-1BBL		Activated B, DC, peritoneal cells
OX-40	CD134	Activation, differentiation, apoptosis	Activated T cells	OX-40L		Activated B cells, cardiac myocytes
Fas	CD95, Apo-1	Activation, apoptosis	Leukocytes	FasL	CD95L, CD178	Activated T cells
AITR	GITR	Costimulation	Treg, T (upregulated)	AITRL	GITRL, TL6	APC

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Product Listing

For ordering information and available formats, please visit www.ebioscience.com. We offer antibodies in the following formats: Purified, FG Purified, Biotin, FITC, PE, PE-Cy5, APC, Cy5, APC-Cy7, PE-Cy7, APC-Cy5.5, PE-Cy5.5, Alexa Fluor[®], and Pacific Blue[®].

Antigen	Human	Mouse	Rat
CD2	RPA-2.10	RM2-5	-
CD3	OKT3, UCHT1, HIT3a	17A2, 145-2C11	eBioG4.18
CD4	OKT4, RPA-T4	GK1.5, RM4-4, RM4-5	-
CD5	UCHT2	53-7.3	HIS47
CD8a	RPA-T8, HIT8a	53-6.7	-
CD11a	HI111	M17/4	-
CD11b	CBRM1/5, ICRF44	M1/70	-
CD11c	3.9	N418	-
CD19	HIB19	eBio1D3, MB19-1, 6D5	-
CD20	2H7	-	-
CD24/HSA	eBioSN3	30-F1, M1/69	-
CD25/IL-2R α	BC96	PC61.5, eBio7D4, eBio3C7	-
CD26	2A6	-	-
CD27	LG.7F9, O323	LG.7F9	LG.7F9
CD28	CD28.6 (blocking), CD28.2 (costimulatory)	37.51	JJ319
CD30	-	mCD30.1	-
CD40	5C3	1C10, HM40-3	-
CD44	IM7	IM7	-
CD54/ICAM-1	HA58	YN1/1.7.4, eBioKAT-1	-
CD62L/L-Selectin	DREG-56	MEL-14	-
CD69/VEA	FN50	H1.2F3	-
CD70/CD27L	-	FR70	-
CD80/B7.1	2D10.4	16-10A1	3H5
CD81/TAPA-1	-	Eat-2	Eat-2
CD83	HB15e	Michel-17	-
CD86/B7.2	IT2.2	PO3.1, GL1	24F
CD90/Thy1	eBio5E10	G7	-
CD90.1/Thy1.1	-	HIS51	HIS51
CD90.2	-	53-2.1, 30-H12	-
CD95/Fas	EOS9.1, DX2	15A7	-
CD122/IL-2R β	-	5H4, TM- β	-
CD134/OX-40	ACT35	OX-86	-
CD137/4-1BB	-	17B5	-
CD150/SLAM	A12 (7D4)	9D1	-
CD152/CTLA-4	eBio20A, 14D3	9H10, UC10-4B9	WKH203
CD153/CD30L	-	RM153	-
CD154/CD40L	24-31	MR1	-
CD178/FasL	NOK-1	MFL3, MFL4	MFL4
CD209/DC-SIGN	eB-h209, polyclonal	5H10, LW06	-
4-1BBL	-	TKS-1	-
AITR/GITR	eBioAITR	DTA-1	-
AITRL/GITRL	eBioAITR-L	-	-
B7-H3	-	M3.2D7	-
B7-H4	H74	eBioMIH29, clone 9, 188	-
BTLA	MIH26	6F7 (blocking), 3F9.D12, 6H6, 6G3, 8F4 (non-blocking)	-
HLA-ABC	W6/32	-	-
HLA-DR	LN3	-	-
ICOS	ISA-3	7E.17G9, C398.4A, 15F9	C398.4A
ICOSL/B7RP-1	MIH12	HK5.3	-
MHC Class I	-	34-1-2S, 28-14-8	-
MHC Class II	-	M5/114.15.2, NIMR-4, 14-4-4S	HIS19, 14-4-4S
NKG2D	1D11 (activating), 5C6 (activating)	A10 (activating), CX5 (blocking), MI-6 (blocking), C7 (blocking)	-
OX-40L	-	RM134L	ATM2
PD-1	eBioJ105, MIH4, J116	J43, RMP1-30, RMP1-14	-
PD-L1/B7-H1	MIH1	MIH5, 1-111A	-
PD-L2/B7-DC	MIH18	TY25, 122	-
RAE-1 γ	-	CX1	-
TCR $\alpha\beta$	IP26	H57-597 (TCR β)	R73
TCR $\gamma\delta$	B1.1	eBioGL3, UC7-13D5	V65
ZAP-70	1E7.2	1E7.2	-