

Role of T cell costimulatory pathways in regulating immune responses

A. GOALS OF THIS LECTURE

The goals of this lecture are to give you an understanding of the role of T cell costimulation in regulating immune responses. T cell costimulatory molecules can provide:

- 1) positive second signals that promote T cell activation
- 2) negative second signals that inhibit T cell responses/induce T cell tolerance

B. OVERVIEW

The initiation and progression of an appropriate immune responses depends upon the tight regulation of lymphocyte activation. The "two-signal" concept of lymphocyte activation was originally proposed to explain how antigen recognition by mature peripheral B cells could result in either of two seemingly opposing outcomes: lymphocyte clonal expansion and antibody production or unresponsiveness (anergy). Bretscher and Cohn developed this model to explain both discrimination of self from non-self, and immunization versus tolerance induction for B cell responses. Lafferty and Cunningham extended this model to T cells. According to this model, T cells require two signals to become fully activated. The first signal, which gives specificity to the immune response, is provided by the interaction of antigenic peptide-MHC complex with the T cell receptor (TCR). The second, antigen-independent costimulatory signal, is delivered to T cells by antigen-presenting cells (APCs) to promote T cell clonal expansion, cytokine secretion, and effector function. In the absence of the second signal, antigen-specific lymphocytes fail to respond effectively, and are functionally inactivated and resistant to subsequent activation to the antigen (anergic). Thus, costimulation, was postulated to have a critical role in determining T cell activation versus anergy. Costimulation is of therapeutic interest because an understanding of these signals may provide methods for blocking undesired T cell responses or stimulating immune responses.

The two signal model is useful but oversimplifies the contribution of signals one and two in several ways. First, there is a quantitative influence of the strength of the TCR signal upon T cell activation and differentiation. T cell activation may occur under conditions of strong TCR stimulation without second signals. Second, there are both positive and negative second signals that can be delivered to T cells. Some negative second signals appear to be necessary for inducing T cell tolerance, whereas positive second signals promote T cell activation. Finally, although the two signal hypothesis was proposed for naïve lymphocytes, the immune response is a dynamic process, and costimulatory signals also can be delivered to antigen-experienced effector and memory T cells.

There are now a large number of T cell costimulatory molecules, with distinct and overlapping functions. One of the current challenges in this area is to understand the functions of each of these T cell costimulatory pathways. Costimulation is provided by three major families: the B7:CD28 superfamily, a TNF:TNFR subfamily that lack death domains, and the CD2 superfamily, as well as some integrins. In this lecture, we will focus on the B7:CD28 superfamily, comparing the roles of pathways within the B7:CD28 superfamily in regulating the activation of naïve and antigen-experienced T cells.

C. B7 : CD28 SUPERFAMILY

The B7-1/B7-2:CD28/CTLA-4 pathway is the best characterized T cell costimulatory pathway and has a critical role in regulating T cell activation and tolerance. Recently, additional B7 and CD28 family members have been identified, and two new pathways have been delineated: one pathway involving ICOS that interacts with a ligand which will be called ICOS ligand but is also known as B7h, GL50, B7RP-1, LICOS, B7-H2, and a second pathway involving the PD-1 receptor that interacts with two new B7 family members, PD-L1 [B7-H1] and PD-L2 [B7-DC]. In addition, there is another B7 homologue, B7-H3 whose receptor remains to be identified, suggesting that there are still additional pathways within the B7:CD28 superfamily to be identified.

Signals through the B7:CD28 superfamily are major regulators of the critical balance between the stimulatory and inhibitory signals required for effective immune responses to pathogens and for maintaining tolerance to self. Key positive and negative second signals are provided by the B7:CD28 superfamily are shown in the Tables below. In this lecture functions of the pathways within the B7:CD28 superfamily will be discussed and compared.

For more information see: Sharpe, Latchman and Greenwald “Accessory Molecules and Co-stimulation” in Fundamental Immunology, 5th edition, W. Paul editor, Lippincott, Williams and Williams ,in press

Table 2. Comparison of B7 family members

	B7-1 (CD80)	B7-2 (CD86)	ICOSL (B7h, B7- H2;B7RP-1)	PD-L1 (B7-H1)	PD-L2 (B7-DC)	B7-H3
% homology	100%	23%	25%	22%	21%	24%
Chromosome						
Human	3q13	3q21	21q22	9p24	9p24	15q24
Mouse	16B, 32.8	16B, 26.9	10C1	19B	19B	9A
Expression						
Lymphoid	B, M, DC, T	B, M, DC, T	B, M, DC, T	B, M, DC, T	DC	M, DC
Non-lymphoid	rare	rare	Fibroblast Endothelial ? others	Endothelial, Tumor cells Many tissues; high in heart, placenta	?	Many tissues; absent in PBLs, Bone Marrow
Kinetics	I; later than B7-2	C & I	C & I	C & I	C & I	I
Receptor	CD28 CTLA-4	CD28 CTLA-4	ICOS	PD-1	PD-1	?
Knockout phenotype	Modest defects in T cell activation; overlap with B7-2	Some Defects in T cell activation; overlap with B7-1	?	?	?	?

Table 2. Comparison of B7 family of costimulatory molecules. B=B cell; M=macrophage;DC=dendritic cell, T=T cell; I= inducible;C=constitutive

Adapted from Sharpe, Latchman and Greenwald “Accessory Molecules and Co-stimulation” in Fundamental Immunology, 5th edition, W. Paul editor, Lippincott, Williams and Williams ,in press