Costimulatory pathways of T-cell activation

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T lymphocytes play an essential role in the defense against several pathogens and in tumor immune surveillance. However, T cells can also trigger autoimmune diseases and acute allograft rejection. Therefore, understanding the mechanisms of activation of T lymphocytes may help develop novel immunomodulators for therapeutic purposes.

T-cell activation results from recognition by the T-cell receptor of a specific antigenic peptide within a specific major histocompatibility complex molecule expressed on antigen-presenting cells (APCs). In addition, naïve T cells express the costimulatory receptor CD28 that binds ligands also expressed on APCs. Coengagement of at least T-cell receptor and CD28 is necessary for naïve T cells to undergo activation, proliferation, and differentiation. Upon activation, T cells transiently up-regulate a number of alternative costimulatory receptors [1]. In addition, recently activated T cells also express inhibitory receptors such as CTLA-4 [2]. PD-1, BTLA, and Fas, the engagement of which may lead to cell-cycle arrest or apoptosis and limits the magnitude and/or duration of an immune response. Mice carrying null mutations of these inhibitory genes all develop different degrees of lymphoaccumulation and autoimmunity.

The ratio of surface versus intracellular expression of CTLA-4, which determines how much CTLA-4 can bind its ligand, is regulated by the phosphorylation status of a tyrosine in its cytoplasmic tail [3–5]. Functionally, CTLA-4 appears to regulate the threshold of T-cell activation, as CTLA-4-deficient T cells require lower levels of antigenic stimulation than CTLA-4 expressing T cells [6]. In addition, the inhibitory effect of CTLA-4 appears to be greater in secondary than in primary stimulation of naïve T cells [6]. We have used several approaches centered on CTLA-4 to inhibit immune responses in vivo. First, targeted cross-linking of CTLA-4 using membrane-bound single-chain anti-CTLA-4 antibody expressed on allogeneic cells effectively down-regulated allograft destruction in a mouse model in vivo [7]. Conversely, transgenically driven constitutive expression of CTLA-4 on T cells significantly delayed acute allograft rejection as well as dramatically reduced disease in an experimental model of autoimmunity (manuscript in preparation). However, the mechanisms by which CTLA-4 inhibits T-cell responses are not completely understood. Collective evidence from different laboratories suggests that CTLA-4 engagement may not only directly inhibit activation of conventional T cells, but also reduce the function of ligand-expressing APCs, and perhaps play a role in the suppressor function of a subset of regulatory T cells. These latter properties may, indirectly, also reduce the function of conventional T cells.

REFERENCES


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