Annu. Rev. Immunol. 2005. 23:515–48
doi: 10.1146/annurev.immunol.23.021704.115611
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First published online as a Review in Advance on January 19, 2005

THE B7 FAMILY REVISITED

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Key Words costimulation, B7, CD28, tolerance

■ **Abstract** The discovery of new functions for the original B7 family members, together with the identification of additional B7 and CD28 family members, have revealed new ways in which the B7:CD28 family regulates T cell activation and tolerance. B7-1/B7-2:CD28 interactions not only promote initial T cell activation but also regulate self-tolerance by supporting $CD4^+CD25^+$ T regulatory cell homeostasis. CTLA-4 can exert its inhibitory effects in both B7-1/B7-2 dependent and independent fashions. B7-1 and B7-2 can signal bidirectionally by engaging CD28 and CTLA-4 on T cells and by delivering signals into B7-expressing cells. The five new B7 family members, ICOS ligand, PD-L1 (B7-H1), PD-L2 (B7-DC), B7-H3, and B7-H4 (B7x/B7-S1) are expressed on professional antigen-presenting cells as well as on cells within nonlymphoid organs, providing new means for regulating T cell activation and tolerance in peripheral tissues. The new CD28 families members, ICOS, PD-1, and BTLA, are inducibly expressed on T cells, and they have important roles in regulating previously activated T cells. PD-1 and BTLA also are expressed on B cells and may have broader immunoregulatory functions. The ICOS:ICOSL pathway appears to be particularly important for stimulating effector T cell responses and T cell–dependent B cell responses, but it also has an important role in regulating T cell tolerance. In addition, the PD-1:PD-L1/PD-L2 pathway plays a critical role in regulating T cell activation and tolerance. In this review, we revisit the roles of the B7:CD28 family members in regulating immune responses, and we discuss their therapeutic potential.

INTRODUCTION

Pathways in the B7:CD28 family have key roles in regulating T cell activation and tolerance and are promising therapeutic targets. These pathways not only provide critical positive second signals that promote and sustain T cell responses, but they also contribute critical negative second signals that downregulate T cell responses (1–7). These negative signals function to limit, terminate, and/or attenuate T cell responses, and they appear to be especially important for regulating

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