

Insufficient costimulation with either B7-1 or B7-2 costimulatory molecules allows activated T cells to escape from the optimal regulation and accelerates mouse model of colitis

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B7-1 (CD80) and B7-2 (CD86) costimulatory molecules are required for optimal T cell activation and survival. At the same time, full activation evokes optimal regulatory mechanisms, such as activation induced cell death, anergy, and induction and upregulation of regulatory molecules such as CTLA-4. To address the idea that insufficient costimulation might generate a subtle condition in which T cells can be activated but can not be regulated properly, we analyzed proliferation, cell death and CTLA-4 expression of activated CD4⁺ T cells which have been co-stimulated with both B7-1 and B7-2, either molecule, or neither molecule.

5x10⁴ of CFSE-labeled CD4⁺CD25⁻ cells (purified from B7-1/2 double deficient mice; >95% naïve CD45RB^{high} cells) were stimulated with various concentrations (0-5.0 μg/ml) of soluble anti-CD3 monoclonal antibody (mAb) and T cell-depleted gamma-irradiated spleen cells from C57BL/6 (B6), with cells from B7-1^{-/-}, B7-2^{-/-} or B7-1/2^{-/-} mice as antigen presenting cells (APC). After four days of culture, B6 APC elicited almost maximal proliferation and CTLA-4 expression even with 0.1 μg/ml of anti-CD3 mAb, while there were few CFSE-diluted cells in the culture with B7-1/2^{-/-} APC. Interestingly, B7 single deficient APC that express either B7-1 or B7-2 induced less but comparable proliferation, despite the failure to induce intracellular CTLA-4, even upon stimulation with 5.0 μg/ml of anti-CD3mAb. Furthermore, IL-2-dependent activation induced cell death that is seen in cultures with B6 APC, but did not occur in those cultures with B7 single deficient APC.

To confirm if these 'dys-regulated' T cells can cause disease in animals, we compared the pathogenesis in a transfer model of mouse colitis using B6, B7-1^{-/-}, B7-2^{-/-} or B7-1/2^{-/-} Rag1^{-/-} mice as recipients. In this model, transferred CD4⁺CD45RB^{high} cells cause chronic colitis in B6.Rag1^{-/-} immune deficient recipients in 6-8 weeks after the transfer. Surprisingly, B7 single deficient recipients developed more severe colitis than Rag1^{-/-} recipients that express both B7 molecules. Inflammation was restricted to the large intestine and persisted until more than 6 weeks post transfer when the recipients were analyzed. Thus, insufficient B7 costimulation could allow activated cells to escape from regulatory processes and accelerate the pathogenesis of autoimmune colitis.