IL-1 alpha and TNF-alpha are required for IL-12-induced development of Th1 cells producing high levels of IFN-gamma in BALB/c but not C57BL/6 mice.

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The development of Th1- or Th2-type responses determines the type of immune response that is elicited in response to Ag. Responsiveness to IL-12 is critical for the development of Th1-type CD4+ T cells required for cell-mediated immune responses. Addition of IL-12 to primary cultures of CD4+ T cells stimulated with OVA and splenocytes or dendritic cells resulted in the development of a Th1 phenotype with the capacity to secrete high levels of IFN-gamma upon restimulation with splenic APC. The present study shows that using dendritic cells to present Ag upon restimulation reveals a requirement for additional cofactors, including IL-1 alpha and TNF-alpha, which were provided by spleen cells but not dendritic cells. Furthermore, these cofactors are required for optimal IL-12-induced Th1 development in BALB/c but not C57BL/6 mice. This differential requirement for such cofactors in IL-12-driven Th1 development may play a role in genetic predisposition to Th1 or Th2 responses to infectious agents.

Adjuvants, Immunologic; physiology; Animal; Antigen-Presenting Cells; immunology; CD4-Positive T-Lymphocytes; metabolism; Cell Differentiation; immunology; Clonal Anergy; genetics; Clone Cells; Comparative Study; Dendritic Cells; immunology; Dendritic Cells; metabolism; Interferon Type II; biosynthesis; Interleukin-1; physiology; Interleukin-12; physiology; Lymphocyte Transformation; genetics; Mice; Mice, Inbred BALB C; Mice, Inbred C57BL; Mice, Transgenic; Receptors, Antigen, T-Cell, alpha-beta; genetics; Species Specificity; Spleen; cytology; Spleen; immunology; Support, Non-U.S. Gov't; Th1 Cells; cytology; Th1 Cells; immunology; Th1 Cells; metabolism; Tumor Necrosis Factor; physiology;
Does B7-1 expression confer antigen-presenting cell capacity to tumors in vivo?

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Tumors engineered to express the costimulatory molecule B7-1 can elicit CD8+ cytotoxic T lymphocyte (CTL)-dependent antitumor responses in immunocompetent mice. It has been postulated that this result reflects direct priming of CTL by the modified tumor in vivo. Previous studies of the immune response to a B7-1- murine colon carcinoma expressing influenza nucleoprotein (NP) as a model tumor antigen have demonstrated the crucial role of bone marrow-derived antigen-presenting cells (APCs) in the priming of NP-specific CTL in vivo. In this system, no evidence of direct CTL priming by tumor was detected. We have performed a similar analysis to determine if B7-1 transfectant of this tumor results in the direct priming of CTL, and to compare this response to that primed by host APCs. When H-2b-->H-2bxd bone marrow chimeras were immunized with a single injection of CT26/NP/B7-1 (H-2d), NP-specific CTL were detected that were restricted to the bone marrow haplotype (H-2b), but not to the tumor haplotype. In contrast, CTL recognizing the NP antigenic epitope in the context of the tumor's major histocompatibility complex were detectable only after multiple immunizations. These results suggest that whereas B7-1+ tumor vaccines result in some degree of direct presentation to CD8+ T cells, the dominant mechanism of CTL priming is through the uptake and presentation of tumor antigens by bone marrow-deprived APCs. However, repeated immunization with B7-1+ tumor cells can efficiently expand the directly primed CD8+ CTL population.

Amino Acid Sequence; Animal; Antigen-Presenting Cells; immunology; Antigens, CD80; biosynthesis; Bone Marrow; immunology; Capsid; biosynthesis; Capsid; chemistry; Capsid; immunology; Cell Line; Clone Cells; Colonic Neoplasms; immunology; Comparative Study; Crosses, Genetic; Epitopes; analysis; Female; Flow Cytometry; Gene Expression; Major Histocompatibility Complex; Male; Mice; Mice, Inbred C57BL; Molecular Sequence Data; Orthomyxoviridae; immunology; Support, U.S. Gov't, P.H.S.; T-Lymphocytes; Cytotoxic; immunology; Transfection; Viral Core Proteins; biosynthesis; Viral Core Proteins; chemistry; Viral Core Proteins; immunology
Cell division during thymic selection was studied with a system in which purified populations of T cell antigen receptor (TCR)- CD4+8+ (double-positive [DP]) cells and fetal thymic epithelial cells (TEC) were reaggregated in tissue culture. In this system, immature DP cells differentiate into mature single-positive (SP) CD4+8- and CD4-8+ TCRhi cells within 3-4 d, indicative of positive selection. By adding the DNA precursor, bromodeoxyuridine, to the cultures and staining cells for bromodeoxyuridine incorporation, T cell division in reaggregation cultures was found to be high on day 1, low on day 2, and high on days 4-5. Cell separation studies established that cell division on day 1 was restricted to DP blast cells. In the absence of blast cells, small DP cells failed to proliferate and differentiated into SP cells without cell division, thus indicating that proliferation is not an essential component of positive selection. This applied to SP cells generated within the first 2-3 d. Surprisingly, the SP cells generated later in culture showed a high rate of cell division; the proliferating SP cells were TCRhi and included both CD4+8- and CD4-8+ cells. Turnover of TCRhi SP cells was also prominent in the normal neonatal thymus and in TEC reaggregation cultures prepared with adult lymph node T cells. We speculate that division of mature SP cells in the perinatal thymic microenvironment is driven by stimulatory cytokines released from TEC. Such proliferation could be a device to expand the mature T cell repertoire before export to the periphery.
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