The Journal of Immunology

IN THIS ISSUE

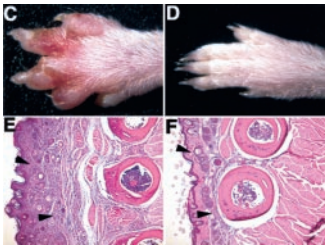
J Immunol 2004; 173:713-714; ;
doi: 10.4049/jimmunol.173.2.713
http://www.jimmunol.org/content/173/2/713

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

IN THIS ISSUE

Reversing the motheaten phenotype



The Ostrowski laboratory previously demonstrated that the Ets2 transcription factor in macrophages from moth eaten mice is constitutively phosphorylated at Thr (aa 72). These mice carry the motheaten viable (*me-v*) mutation of the hemopoietic cell phosphatase gene (Hcph$^{me\text{-}v/me\text{-}v}$) and suffer from an arthritis-like inflammation of the joints. In a paper from the same laboratory, Wei et al. (p. 1374), looked at the role of Ets2 phosphorylation in motheaten pathology. They introduced a mutated Ets2 gene encoding Ala at aa 72 into Hcph$^{me\text{-}v/me\text{-}v}$ mice. Mice homozygous for both genes (Ets2$^{A72/A72}$ Hcph$^{me\text{-}v/me\text{-}v}$) were similar to wild-type mice in having greater than six times the survival rate at 100 days, twice the body weight, and no joint inflammation compared with Hcph$^{me\text{-}v/me\text{-}v}$ homozygotes. Whereas the Hcph$^{me\text{-}v/me\text{-}v}$ animals developed fatal pneumonitis from an accumulation of macrophages and neutrophils in their lungs, the double homozygotes did not accumulate macrophages in their lungs and remained healthy. However, bone marrow-derived macrophages from the double homozygotes lost some of the apoptotic resistance of Hcph$^{me\text{-}v/me\text{-}v}$ macrophages. A number of inflammation-related genes expressed in alveolar and peritoneal macrophages from Hcph$^{me\text{-}v/me\text{-}v}$ mice were found by quantitative real time PCR to be down-regulated in macrophages from the double homozygotes. The authors propose that Hcph negatively regulates Ets2 phosphorylation; constitutive phosphorylation of Ets2 in motheaten mice results in increased expression of genes responsible for the severe inflammatory phenotype.

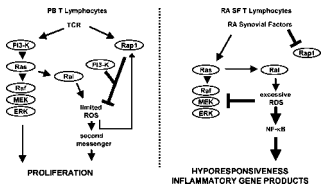
Tumor-associated glycoproteins block CD4$^+$ T cell surveillance

Although CD4$^+$ T cells are important for optimal antitumor immunity, there is no information as to how tumors evade detection by them. Gutzmer et al. (p. 1023) looked at interference in immune surveillance by two tumor-associated Ags, the human type I integral membrane glycoprotein, GA733–2, and its mouse homologue, mEGP. Murine dendritic cells (DCs) transduced with an adenovirus vector expressing mEGP had a decreased ability to stimulate allogeneic CD4$^+$ T cells in MLR compared with control DCs; their ability to respond to anti-CD3 Ab or Con A was not affected. Ag-specific T cells were unable to recognize mEGP-transduced DCs pulsed with the specific Ag or antigenic peptide. The inhibitory response was limited to Ags presented by MHC class II molecules, as mEGP-transduced DCs were able to stimulate T cell proliferation to Ags presented by MHC class I molecules. Similar results were found for human DCs transduced with a vector expressing GA733–2 and tested against primary CD4$^+$ T cells from the same human donors. Mouse DCs exposed in vitro to homogenates of mEGP-transduced cells only, or containing a peptide presented by MHC class II molecules, lost general and specific CD4$^+$ T cell stimulatory activities, respectively. Splenocytes from mice injected with DCs transduced with adenovirus-expressing mEGP had diminished in vitro T cell proliferative responses to adenovirus Ags compared with vector controls. The authors propose that mEGP and GA733–2 interference with MHC class II-dependent Ag presentation by DCs represents a novel mechanism of tumor evasion.

IL-21 regulation of cell-mediated tumor immunity

Activated CD4$^+$ T cells produce IL-21 which shares the common γ-chain receptor subunit with IL-2 and IL-15 to influence CD8$^+$ T cell responses. Moroz et al. (p. 900) directly compared the effectiveness of these cytokines to promote survival of C57BL/6 (B6) mice injected with syngeneic thymoma cells expressing OVA Ag. Injection of IL-21 beginning 2 days after tumor injection led to 20–30% of the animals surviving greater than 120 days. Tumor-injected mice that received IL-2 or IL-15 survived to day 60 and day 80–90 compared with 40 days for untreated controls. The increased survival benefit was lost if IL-21 recipients had been depleted of CD8$^+$ T cells; depletion of other cell types had no effect on survival. All IL-21-treated, long-term survivors also survived rechallenge with the same tumor but succumbed to challenge with an unrelated tumor. Significant numbers of CD8$^+$ T cells were detected by OVA-tetramer staining at 45 days after tumor challenge only in the IL-21-treated group; highest lytic activity was seen at 30 days for CD8$^+$ T cells from animals treated with IL-21 and IL-15. Adoptively transferred naive T cells expressing OVA were found in the peritoneal cavity of IL-21-treated mice 3–4 days after tumor challenge; IL-21 stimulated greater expansion and less apoptosis of these cells compared with IL-2. The results indicate that IL-21 enhances survival of mice to tumors by promoting longevity of activated tumor-specific CD8$^+$ T cells.

Rap1 regulates oxidative stress in rheumatoid arthritis synovial T cells



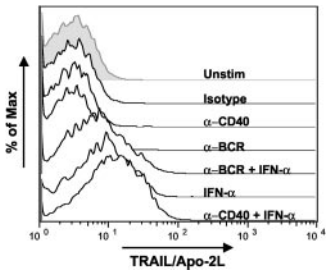
T cell receptor signaling is mediated by reactive oxygen species (ROS). The GTPase, Ras, is known to participate in signaling in T lymphocytes, and a close relative, Rap1, is known to suppress transformation by Ras. However, there is no information about Ras and Rap1 interactions in activated T cells. Remans et al. (p. 920) generated a series of dominant active and dominant negative mutants of Ras, Rap1, and other small GTP binding proteins to look at ROS in activated Jurkat T cells and in T cells from the synovial fluid (SF) of patients

0022-1767/04/$02.00

with rheumatoid arthritis (RA). They found that Ras signaling stimulated ROS production via the small GTPase, Ral. Transfection of Jurkat cells with an inactive Rap1 mutant showed that Rap1 signaling was required for down-regulation of ROS generation induced by agonists; constitutive expression of an active Rap1 mutant blocked agonist-induced or Ral-induced ROS production. TCR stimulation of SF T cells from RA patients failed to increase Rap1 activation. Moreover, basal levels of activated Rap1 were decreased in those SF T cells, whereas Rap1 was activated in stimulated peripheral blood T cells from RA patients. RA SF T cells had constitutive Ras activation but ERK activation was blocked following stimulation. Transfection of a variety of Rap and Ras mutants into SF T cells restored kinase responsiveness to TCR stimulation and decreased the enhanced rate of ROS production. The authors suggest that the oxidative stress seen in RA SF T lymphocytes is a result of defects in Rap1 activation and suppression of GTPase signaling.

Stimulating B cells to kill

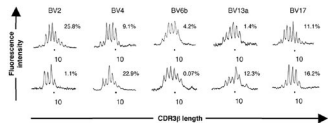
CpG oligodeoxynucleotides (CpG ODN) are known to stimulate PBMCs and to induce antitumor immune responses. However, the molecular mechanism by which CpG ODN act had not been defined. Kemp et al. (p. 892) found that PBMCs stimulated with CpG-A ODN, that activate plasmacytoid dendritic cells, produced 200-fold higher levels of IFN-α and had greater tumoricidal activity than PBMCs stimulated by CpG-B ODN, that activate B cells. CpG-A ODN or IFN-α induced expression of TRAIL/Apo-2L on PBMCs, including B cells. Purified TRAIL/Apo-2L-expressing B cells lysed tumor cells; addition of TRAIL-R2:Fc or IFN-α neutralizing antiserum blocked the tumor cell lysis. TRAIL/Apo-2L expression was not induced by direct stimulation of purified B cells by CpG-A ODN. However, incubation of purified B cells with IFN-α stimulated a modest level of TRAIL/Apo-2L expression that was enhanced by adding an agonist, CD40 mAb, with the IFN-α. The authors conclude that IFN-α produced by CpG ODN stimulation of PBMCs acts in concert with CD40-CD40L to induce B cells to kill tumor cells via a TRAIL/Apo-2L-dependent mechanism.



Invariant NKT cells and infectious tolerance

Murine invariant NKT (iNKT) cells express an invariant TCR containing the Vα14 and Jα18 gene segments, recognize glycolipids in a CD1d-restricted manner and have been implicated in promoting peripheral T cell tolerance. Roelofs-Haarhuis et al. (p. 1043) determined the role of iNKT cells in nickel (Ni)-induced tolerance. C57BL/6 (B6) wild-type mice and J$\alpha18^{-/-}$ B6 mice, that lack iNKT cells, were sensitized to Ni by intradermal injections. Both strains exhibited comparable levels of ear swelling when challenged by injection with Ni salts and H_2O_2. However, only B6 mice were tolerized by oral administration of Ni before sensitization and rechallenge. T cell-depleted spleen cells, but not splenic T cells, from J$\alpha18^{-/-}$ mice treated orally with Ni induced tolerance in B6 recipients after transfer. In contrast, splenic T cells, but not T cell-depleted spleen cells, from orally tolerized B6 donors transferred tolerance into naive J$\alpha18^{-/-}$ recipients. Infectious tolerance experiments showed that T cell-depleted spleen cells from orally treated J$\alpha18^{-/-}$ mice spread Ni tolerance to naive T cells in B6 recipient animals, and those B6 regulatory T cells, in turn, prevented sensitization of naive T cells when transferred into a second set of B6 recipients. No infectious tolerance was induced if the first recipients were J$\alpha18^{-/-}$ mice or if the donors were CD1$^{-/-}$, IL-4$^{-/-}$, or IL-10$^{-/-}$. Moreover, tolerance in J$\alpha18^{-/-}$ mice could be induced by cotransfer of tolerogenic B6 T cell-depleted spleen cells and naive B6 spleen cells containing CD4$^+$ T cells. The authors conclude that signals from iNKT cells are required for T cell-depleted spleen cells to generate regulatory T cells in this model of infectious tolerance to Ni.

Regulatory T cells and antimelanoma responses



Immunotherapy directed at treating patients with metastatic melanoma has had limited success. These treatment failures could be due, in part, to interference by CD4$^+$CD25^{high} regulatory T (T_{reg}) cells in the local antitumor immune response. Viguier et al. (p. 1444) found that the frequency of T_{reg} cells in metastatic lymph nodes (LNs) from 12 patients with stage III melanoma was greater than that in tumor-free LNs or in PBMCs from metastatic melanoma patients and healthy donors. The T_{reg} cells had an activated phenotype, including intracellular and surface expression of CTLA-4, and expressed high levels of transcription factor Foxp3 mRNA. Sorted T_{reg} cells from metastatic melanoma patients proliferated poorly and did not produce IL-2 or IFN-γ when stimulated. The T_{reg} cells inhibited the proliferation and cytokine production of stimulated CD4$^+$CD25$^-$ T cells or CD8$^+$ T cells; the suppressive activities were abolished by preventing cell contact via a transwell or by pretreatment of the T_{reg} cells with anti-IL-10, anti-TGF-β_{1-3}, or anti-CTLA-4 Abs. Only T_{reg} cells from LNs with substantial tumor invasion produced immunosuppressive cytokines IL-10 and/or TGF-β_1 after stimulation. Immunoscope analyses indicated a highly diverse set of TCR Vβ families among CD4$^+$ T cells from metastatic and tumor-free LNs. The authors suggest that increased numbers of T_{reg} cells in metastatic LNs down-regulate antitumor responses in melanoma patients, resulting in poor response to immunotherapy.

Summaries written by Dorothy L. Buchhagen, Ph.D.