The Journal of Immunology
IN BRIEF | APRIL 01 2008
IN THIS ISSUE FREE

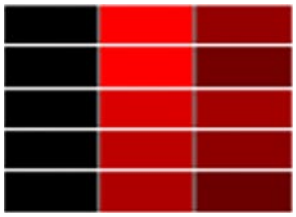
Online Issn: 1550-6606
Print Issn: 0022-1767

2008

J Immunol (2008) 180 (7): 4349–4350.
https://doi.org/10.4049/jimmunol.180.7.4349

IN THIS ISSUE

FoxP3 Interaction with RORα



The molecular mechanisms that regulatory T cells (Tregs) use to suppress immune responses are still unclear. Humans express at least two isoforms of transcription factor forkhead box 3 (FoxP3) in Tregs, a full-length form and a splice variant lacking exon 2, both of which are equally induced upon $CD4^+CD25^-$ T cell stimulation. Using a yeast two-hybrid screen, Du et al. (p. 4785) determined that part of FoxP3 transcriptional suppression is mediated through its interaction with the retinoic acid receptor-related orphan receptor (RORα). FoxP3 and RORα colocalized in the nucleus of transfected cells, but the full-length form of FoxP3 was necessary for interaction with RORα. Without the LxxLL motif located in exon 2 of the FoxP3 transcript or the AF2 motif in RORα, there was no interaction with RORα and transcriptional repression by FoxP3 was abolished. FoxP3 transcriptional control was not dependent on DNA binding, as loss of the forkhead binding domain had no effect. RORα regulates the expression of Th17-type cytokines in T cells such as IL-17, IL-22, and CXCR3, the transcription of which were repressed by expression of full-length FoxP3. The authors have executed an elegant study demonstrating an important mechanism by which FoxP3 mediates immune regulation.

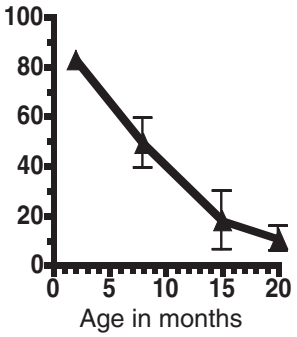
Transpresented IL-15

Mice deficient in IL-15 or IL-15Rα lack peripheral memory $CD8^+$ T cells. IL-15 must be immobilized to its high affinity receptor IL-15Rα and transpresented to target $CD8^+$ T cells expressing CD122 and CD132 for maximal effectiveness. This can occur on the surface of an activated dendritic cell (DC). Kokaji et al. (p. 4391) used immobilized IL-15 on cell-sized microspheres to precisely determine how IL-15 affects peripheral T cell memory without the confounding effect of other costimulatory molecules. The authors found that immobilized IL-15 in combination with TCR stimulation through anti-CD3ε or peptide MHC complexes induced memory $CD8^+$ T cell proliferation and IFN-γ and granzyme B (grB) expression more effectively than soluble IL-15. Both in vitro experiments and lymphocytic choriomeningitis virus infection in IL-15Rα$^{-/-}$ mice demonstrated that central memory (T_{CM}) $CD8^+$ T cells were more sensitive than effector memory (T_{EM}) cells to the proliferative and grB expression effects of transpresented IL-15. Taken together, these experiments show that $CD8^+$ T cell memory responses are dependent on transpresented IL-15 for optimal recall and proliferation.

IL-7-Driven iNKT Differentiation

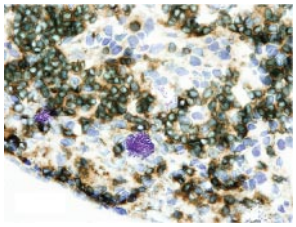
Considered to be innate lymphocytes, invariant NKT cells (iNKT) express an effector-memory phenotype that is independent of foreign Ag stimulation. de Lalla et al. (p. 4415) determined in human fetal and neonatal iNKT cells that differentiation of this innate effector phenotype is driven by exposure to IL-7. Whereas human iNKT cells express a phenotype at the time of birth that correlates with memory and priming ($CD45RO^+$ and $CD44^{high}$), there is no effector cytokine expression from these cells upon ex vivo stimulation. The authors found that differentiation of iNKT cells occurs during fetal development with epigenetic derepression at the *IL4* and *IFNG* loci and activation of GATA-3 and T-bet. Unlike murine iNKT development where differentiation is driven by IL-15, human iNKT thymic effector function matures with IL-7. This occurs because both fetal and neonatal iNKT cells have increased expression and signaling sensitivity through the IL-7Rα-chain compared with ordinary T cells. Thus, the authors have identified IL-7 as the critical signal for completing the differentiation of iNKT cells that occurs in the absence of foreign Ag.

Aged $CD4^+$ T Cells



Older individuals are more at risk for infection because their naive $CD4^+$ T cells are less responsive than in youth. Using OT-II TCR transgenic mice, Jones et al. (p. 4465) have determined that this dysfunction is related to postthymic survival in the aged periphery. In aging OT-II mice (18–24 mo old), deletion of naive $V\beta5^+$ transgenic $CD4^+$ T cells is apparently mediated by an endogenous superantigen. Thus, the number of recent thymic emigrants in the periphery is comparable to that of younger mice (6–10 wk of age), and this compartment is enriched for cells that have reduced postthymic longevity. These cells with reduced postthymic longevity demonstrated in vitro defects in response to Ag; however, adoptive transfer of these cells into syngeneic hosts caused them to regain the ability to respond to IL-2 and provide B cell help. When the authors analyzed $CD4^+$ T cells from aged HNT mice that had extended postthymic longevity, they found the same defect both in vitro and in vivo. Thus, the longer the $CD4^+$ T cell survives outside the thymus in an aging mouse, the more dysfunctional it will be.

Solar-Powered Mast Cells



Irradiation of the skin through UV exposure leads to immunosuppression, production of Th2 cytokines, and the formation of $CD4^+CTLA\text{-}4^+$ regulatory T cells. However, the immediate events that lead to these adaptive responses have yet to be defined. Byrne et al. (p. 4648) demonstrated that skin mast cells migrated to draining lymph nodes (DLN) 24 h after exposure to UV irradiation and that this migration was dose dependent. The authors engrafted GFP^+ skin onto mice and saw an increased number of GFP^+ mast cells in the DLN after UV exposure. These mast cells preferentially localized to the $CD19^+$ regions of the DLN, a result of UV-induced expression of CXCL12 on B cells in the lymph node. This chemokine is the ligand of CXCR4, and treatment of UV-irradiated mice with a CXCR4 antagonist, AMD3100, both stopped mast cell migration to the lymph node and rescued the ability of the mice to develop DNFB-mediated contact hypersensitivity. Taken together, these results elucidate the early events following UV exposure that lead to mast cell-mediated immunosuppression.

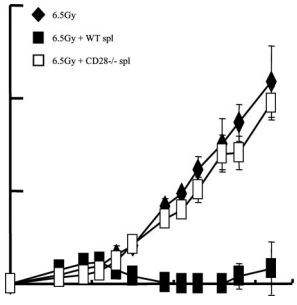
Treg Suppression of Anaphylaxis

The prevalence of allergic disease has steadily increased over time, and understanding the mechanism of anaphylactic reactions to innocuous environmental Ags could lead to controlling this increase. Scabeni et al. (p. 4433) have developed a model to induce anaphylaxis in SJL mice immunized and challenged with a self-peptide, myelin proteolipid protein 139–151 (PLP139–151), that is not expressed in the thymus. Mice similarly immunized and challenged with another thymically-expressed fragment, 178–191 (PLP178–191), did not develop anaphylaxis. Challenge with PLP139–151 after immunization induced anaphylaxis as well as increasing IgG1 and IgG3, increasing IFN-γ, and lowering IL-10 when compared with PLP178–191-challenged mice. However, no differences were found in the number of $CD4^+CD25^+$ regulatory T cells (Tregs) produced in mice treated with either peptide regimen, and both sets of Tregs were effective at suppressing naive $CD4^+CD25^-$ T cells. The Tregs from mice immunized and challenged with PLP178–191 were capable of suppressing Ag-induced proliferation of effector $CD4^+CD25^-$ T cells, and PLP178–191 Tregs could be induced to express higher levels of intracellular FoxP3 than PLP139–151 Tregs. Depleting Tregs in PLP178–191-treated mice led to an increase in the anaphylactic response in these mice. The authors demonstrated that Tregs developed with naturally occurring thymic peptides control the development of anaphylaxis to self.

Proinsulin and IGRP-Driven Diabetes

Transgenic NOD mice that have $CD8^+$ T cells with a TCR specific for residues 206–214 of islet-specific glucose-6-phosphate catalytic subunit related protein (IGRP) are designated as NOD8.3 and develop an accelerated form of diabetes. Krishnamurthy et al. (p. 4458) crossed these NOD8.3 mice with mice tolerant to proinsulin (NOD-PI) and found that the NOD-PI/NOD8.3 mice were protected from diabetes, with reduced insulitis and lower titers of anti-insulin Abs. Despite this protection, NOD-PI/NOD8.3 mice had the same number of $IGRP_{206-214}$-specific T cells as NOD8.3 mice, and these cells were functional in in vitro assays. This demonstrated that tolerance to proinsulin was enough to control the $CD8^+$ T cells specific for $IGRP_{206-214}$. Protection from diabetes was reversed by inducing inflammation in the islets through anti-CD40 agonist Ab treatment or by administering streptozotocin. The authors demonstrate that tolerance to a primary Ag can control the effects of other Ag-specific T cells.

Costimulation for Tumor Attack



Adoptive transfer of T cells into lymphopenic mice has been shown to induce tumor regression, but the mechanism responsible for this homeostatic proliferation-induced effect has not been fully elucidated. Suzuki et al. (p. 4596) determined that, although costimulation via CD28 is not required for homeostatic proliferation, CD28 signaling is required for the antitumor effect. The authors first transferred different populations of T cells into irradiated mice challenged with fibrosarcoma cells and found that naive $CD8^+$ T cells mediated the antitumor response. Transfer of CD28-deficient T cells or blockade of B7 allowed homeostatic proliferation of donor T cells but did not result in tumor rejection. Analysis of $CD8^+$ T cells in the presence or absence of CD28 signaling demonstrated that CD28 was required for the emergence of a small fraction of highly proliferating tumor Ag-specific $CD8^+$ T cells. Interestingly, these highly proliferating cells developed an effector memory phenotype, whereas the cells proliferating in a CD28-independent fashion acquired a central memory phenotype. IL-2 administration could not rescue the antitumor response in the absence of CD28 signaling but could augment CD28-dependent tumor regression. These data clarify the requirements for effector T cell development under lymphopenic conditions and provide valuable insights that may be relevant to cancer treatment.

Summaries written by Kira R. Gantt, Ph.D.