The Journal of Immunology

IN THIS ISSUE

J Immunol 2008; 181:2939-2940; ;
doi: 10.4049/jimmunol.181.5.2939
http://www.jimmunol.org/content/181/5/2939

Supplementary Material http://www.jimmunol.org/content/suppl/2008/08/19/181.5.2939.DC1

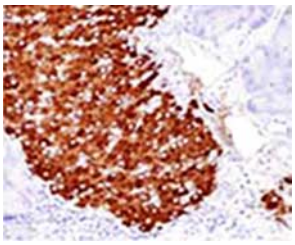
The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

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

THE JOURNAL OF IMMUNOLOGY

In This Issue

A Master Immune Modulator



T lymphocyte differentiation has been thought to be a one-way process; once a naive $CD4^+$ T cell matures into a helper (Th) or T regulatory (Treg) cell, the cell's fate is set. Radhakrishnan et al. (p. 3137) have demonstrated that this fate can be reversed. They found that dendritic cells (DC) treated with an Ab (B7-DC XAb) that crosslinks DC by binding to B7-DC/PD-L2 could reprogram $Foxp3^+$ Treg into T effector cells. The authors designated DC treated with B7-DC XAb as DC^{Xab}. Both in vitro and in vivo interactions between DC^{Xab} and Treg mediated an Ag-specific reduction in FoxP3 expression. The effects of DC^{Xab}:Treg interactions were dependent on the presence of IL-6 and resulted in functional effector T cells. These new effector cells expressed IL-17, TNFα, and IFN-γ but could no longer suppress T cell responses or secrete IL-10 and TGF-β. Mice treated with a vaccine including DC^{Xab} were protected from lethal melanoma while mice treated with the same vaccine including IL-6-deficient DC^{Xab} were not, confirming the necessity of IL-6 and indicating that ex vivo treated DC can reverse the fate of host cells in vaccinated recipients. Transfer of DC^{Xab} into RIP-OVA mice induced diabetes, yet treating wild-type mice with B7-DC XAb did not generate autoimmunity. Thus, activated DC can reprogram Treg into Th17 effector cells and break tolerance to self-Ags, thereby promoting autoimmunity but also potentially protecting against tumor growth.

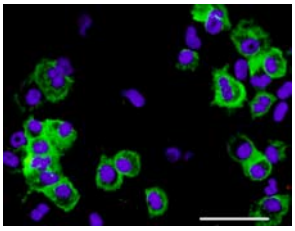
FOXO1, Bringing T Cells Home

Forkhead box O 1 (FOXO1) belongs to a family of transcription factors that act as tumor suppressors, promote stress resistance, and induce apoptosis in lymphocytes. Activation of the PI3K pathway, through either Ag stimulation or growth factors, causes FOXO1 to move from the nucleus to the cytosol. This translocation abrogates the transcriptional activity of FOXO1 and promotes cell growth. In this issue, Fabre et al. (p. 2980) have found that FOXO1 also controls T cell migration through control of L-selectin expression. The transcriptional control of this essential T cell homing molecule requires the FOXO1 DNA-binding domain and FOXO1 localization to the nucleus. Through microarray analysis, the authors found that the sphingosine-1-phosphate receptors EDG1 and EDG6, known regulators of lymphocyte trafficking, were transcriptionally increased with FOXO1 binding. FOXO1 also bound the promoter of Krüppel-like factor 2 (KLF2), which also controls T cell migration and homing. The authors conclude that the PI3K pathway controls another T cell function through FOXO1, the coordination of the transcription and regulation of human T lymphocyte homing molecules.

EBF1 Regulating Networks

Early B cell development from hematopoietic stem cells is a hierarchical process controlled by transcription factors. EBF1, a helix-loop-helix protein, has been shown to be indispensable to this process, but its function was previously unknown. Zandi et al. (p. 3364) have determined that EBF1 is necessary for B lineage priming through specific transcriptional control of relevant genes. The authors transplanted EBF1-deficient fetal liver cells into irradiated recipient mice and found that common lymphoid progenitors (CLPs) and $B220^+CD43^+AA4.1^+$ candidate precursor B cells were generated. However, while the isolated CLPs were able to generate T lymphocytes, B lineage development was blocked. EBF1-deficient CLPs had a reduction in IgH recombination compared with wild type and lacked transcription of the B lineage-associated genes *Pax5*, *Pou2af1* (*OcaB*), and *FoxO1*. Electrophoretic mobility shift and reporter assays revealed that these transcription factors contained functional promoter binding sites for EBF1. Thus EBF1 seems to be regulating a network of transcription factors that drive the B lymphocyte development program.

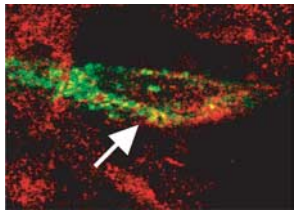
Making a Bid for UVR-Induced Tolerance



Apoptosis is necessary for clearance of UV radiation (UVR)-damaged keratinocytes and for maintenance of healthy skin. However, what role UVR-induced apoptosis plays in immune tolerance and suppression is unclear. Previous work from this group showed that mice lacking the proapoptotic Bid (BH3-interacting death domain protein) have Langerhans cells (LCs) that are resistant to apoptosis and increase immune responses. In this study, Pradhan et al. (p. 3077) have examined the response of Bid-deficient mice to acute UVB irradiation. Bid-deficient mice exposed to UVR had fewer apoptotic cells and greater numbers of epidermal LCs compared with wild-type mice; this indicated that UVR-induced keratinocyte and LC apoptosis can be defined as mitochondrial-associated type II apoptosis. UVR-induced tolerance was absent in Bid-deficient mice in response to hapten or contact hypersensitivity reagents. Immune responses at the site of skin sensitization were similar or increased in the Bid-deficient

animals compared with wild type. After Bid-deficient mice underwent UVR exposure, greater numbers of LCs accumulated in lymph nodes than in wild-type animals. Taken together, the data demonstrated that Bid is necessary for UVR-induced immune tolerance and is a critical part of keratinocyte and LC UVR-initiated apoptosis.

For Whom the Fish Tolls



The fugu fish, otherwise known as *Takifugu rubripes* or puffer fish, is best known as the source of a prized dish in Japanese cuisine to be eaten only after careful preparation by a licensed chef. In Matsuo et al. (p. 3474) this teleost fish is the source of a novel Toll-like receptor, TLR22. The authors identified this novel molecule as being expressed on the surface of fish and amphibian cells, but its expression is restricted to aquatic inhabitants. Fugu TLR22 (fgTLR22) recognized dsRNA on the cell surface and recruited the Toll-IL-1 receptor homology domain-containing adaptor protein 1 (fgTICAM-1) upon ligation. fgTLR3, which also bound the fgTICAM-1 adaptor and recognized dsRNA, was shown to reside in the endoplasmic reticulum. The fgTICAM-1 adaptor acted as a scaffold for IFN signaling, translocating from the TLR to the cytosolic signalosome after TLR ligation. Through fgTICAM-1, fgTLR22 and fgTLR3 responded to aquatic viruses through IFN signaling and allowed fish to develop a protective immune response. The authors propose that fgTLR22 acts as a functional replacement for mammalian cell surface TLR3 and demonstrate a surveillance mechanism against viral challenge in the aquatic environment.

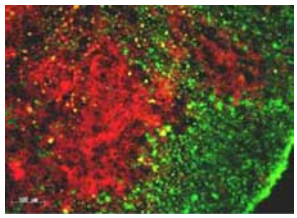
Why One Needs the Surrogate Light Chain

Early progenitor B cells that carry a productive VDJ rearrangement create an Ig μ heavy chain (μHC) that assembles with the surrogate light chain (SLC) and other molecules to form a surface-expressed, pre- or immature B cell receptor (pre-BCR). While signals through this complex enhance the proliferation and differentiation of pre-B cells, the exact function of the SLC component has remained unclear. Although SLC-deficient mice have mature B cells, they are generated at lower numbers than wild type, a defect thought to be due to reduced proliferation of large pre-B cells. To clarify the function of the SLC, Vettermann et al. (p. 3232) examined the SLC N-terminal non-Ig-like λ5 (unique) tail through mutational analysis to determine its function. Transgenic mice with mutated pre-BCRs either lacking the λ5 unique tail or with all of the positively charged amino acids changed to alanine were created. Pre-BCRs were found to be expressed at the cell surface at similar levels in the mutants as in wild type. The authors found reduced numbers of μ H chain-positive pre-B cells and mature B cells in both strains of mice. While differentiation of pre-B cells occurred in the mutant mice, the SLC λ5 tail was necessary for proliferative responses and for binding to stromal cell self-Ags (i.e., heparan sulfate). Unlike previous work, which implied that the SLC was dispensable and could be replaced with early expression of a conventional L chain, this work confirmed that the non-Ig-like tail of the SLC λ5 increases the primary Ab repertoire through autoreactive signaling and proliferation of pre-B cells.

Helping a Friend?

Friend virus (FV), a murine retrovirus, is responsible for erythroleukemia in susceptible mice and otherwise causes persistent infection in all others. The recent discovery that most FV laboratory stocks have been carrying the coinfecting lactate dehydrogenase-elevating virus (LDV) has made the work of Marques et al. (p. 3432) particularly relevant, as they examined the effect of coinfecting mice with these two viruses. Congenic C57BL/6 mice, normally resistant to FV leukemia development, were engineered with the introduction of the FV susceptibility 2 (*Fv2*) gene (B6.A- *Fv2*^{s}). The authors found that B6.A- *Fv2*^{s} mice remained resistant to FV-mediated splenomegaly upon infection and could control FV infection with Ab and T cell responses. However, coinfection with LDV made the B6.A- *Fv2*^{s} mice highly susceptible to FV infection and acute splenomegaly by delaying anti-FV neutralizing Ab production and causing polyclonal B cell activation. In fact, pretreatment of B6.A- *Fv2*^{s} mice with LPS or anti-IgM to cause polyclonal B cell activation mimicked the effect of LDV coinfection and rendered mice susceptible to FV infection. The authors conclude that FV susceptibility can be determined by immune activation caused either by a coinfecting virus or another mechanism.

Splenic Apoptosis and Sepsis



The intracellular DNA-binding protein high mobility group box1 (HMGB1) is a critical molecule in mediating lethal sepsis. Apoptotic cells have been shown to activate macrophages that then release HMGB1 with downstream effects including fever, changes in intestinal barrier integrity, and tissue injury. Previous work has shown that the administration of Z-VAD-FMK, a broad-spectrum caspase inhibitor, to animals with polymicrobial sepsis reduced HMGB1 levels and suppressed the sepsis-induced apoptosis found in the spleen and thymus. Huston et al. (p. 3535) examined whether splenic apoptosis contributed to HMGB1 release in sepsis. They found that mice that had undergone splenectomy with polymicrobial sepsis had reduced systemic HMGB1 release, maintained a Th1 cytokine response profile, and had increased survival. Treatment of splenectomized mice with polymicrobial sepsis with the caspase inhibitor Z-VAD-FMK increased serum HMGB1 levels and failed to protect against lethality. The authors conclude from these data that apoptosis in the spleen is responsible for the HMGB1 release seen in polymicrobial sepsis.

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