# In This Issue

*J Immunol* 2011; 186:6645-6646; ;
doi: 10.4049/jimmunol.1190022
http://www.jimmunol.org/content/186/12/6645



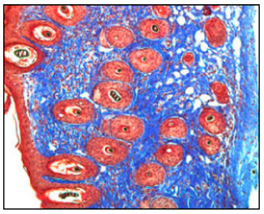
*The Journal of Immunology* is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

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

THE JOURNAL OF IMMUNOLOGY

# In This Issue

## Facilitating Fibrosis



Atopic dermatitis (AD) is a common inflammatory skin disease that involves Th2 activity and skin fibrosis. In a murine model of AD induced by transgenic overexpression of IL-13 in the skin, the cytokine thymic stromal lymphopoietin (TSLP) was upregulated. Oh et al. (p. 7232) have now investigated TSLP's role in skin fibrosis in this model. Turning off the transgenic expression of IL-13 after development of AD caused a decrease in skin inflammation, yet skin fibrosis proceeded unhindered, indicating that fibrosis progression was IL-13 independent. Use of a neutralizing Ab to TSLP or genetic deletion of the TSLPR reduced collagen deposition and fibrosis, compared with controls, and did so independent of IL-13 activity. Fibrocytes, a recently identified cell type bearing markers for both hematopoietic cells and myofibroblasts, accumulated in the skin during IL-13–induced AD through a mechanism requiring TSLP activity. Fibrocytes also accumulated in human AD lesions. In mice, these fibrocytes were found to express the TSLPR, and TSLP directly stimulated their differentiation and production of collagen. This study reveals important participants in the progression of skin fibrosis in IL-13–induced AD that may provide new ideas for therapeutic approaches to this common disease.

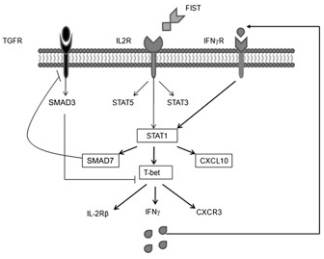
## Peptide CAPacity

Cytoplasmic Ags, which are typically presented by MHC class I molecules, can also be presented by MHC class II through indirect presentation, a process that is not yet fully understood. Because professional APCs are thought to acquire cytoplasmic Ags via phagocytosis of dying allogeneic or infected cells, the class I Ag-processing machinery is presumed to remain uninvolved in indirect presentation. However, Dragovic et al. (p. 6683) have identified an important role for several participants in the cytosolic Ag-processing (CAP) pathway in the regulation of this process. Analysis of indirect presentation of Ags derived from an alloantigen and from *Listeria monocytogenes* demonstrated that proteasomes, TAP, and ERAAP (ER-associated aminopeptidase associated with Ag processing) impaired class II-restricted presentation of cytoplasmic Ags. This impairment did not involve competition between class I and II molecules for Ag, enhanced autophagy, or ER-associated degradation. Instead, the CAP machinery induced quantitative differences in the amount of class II-restricted Ag presented. In addition, efficient indirect presentation of alloantigen was found to require the chaperones heat shock protein 90 and calreticulin. Thus, by controlling the quantity of cytosolic Ags available for class II-restricted indirect presentation, the CAP machinery regulates the magnitude of the resultant T helper cell responses.

## Seeing Clearly with IL-17A

Regulatory T cell (Treg) induction in the cornea is important for maintaining immune privilege following corneal allograft transplantation. The proinflammatory cytokine IL-17A generally acts at cross purposes to Tregs and therefore would be expected to exacerbate allograft rejection. Surprisingly, Cunnusamy et al. (p. 6737) found that IL-17A was required for the survival of corneal allografts. IL-17A blockade did not affect Th1 responses or the induction of anterior chamber-associated immune deviation. Instead, IL-17A produced by $CD4^+CD25^-$ T cells promoted $CD4^+CD25^+$ Treg-mediated suppression of effector $CD4^+$ T cells. These Tregs were Ag specific and suppressed the efferent phase of the alloimmune response via a cell contact-dependent mechanism requiring the presence of IL-17A. Interestingly, blockade of IL-17A and CD25 in mice with long-term surviving corneal allografts did not cause allograft rejection, suggesting that Treg-mediated suppression was transient and necessary only at early time points posttransplantation. This study demonstrates that rather than promoting inflammation and graft rejection, IL-17A is important for Treg induction and the consequent acceptance of corneal allografts.

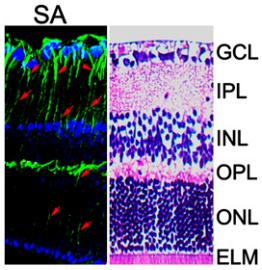
## A FISTful of Antitumor Activity




Tumor-derived TGF-β promotes angiogenesis and inhibits the antitumor immune response. In this issue, Penafuerte et al. (p. 6933) developed an antitumor chimeric protein, designated FIST, consisting of IL-2 fused to the extracellular domain of TGF-β receptor II. This reagent acted as a decoy receptor for TGF-β, "trapping" it to prevent its prooncogenic activity, and at the same time stimulated antitumor immunity via IL-2. Specifically, stimulation of IL-2–responsive lymphocytes with FIST induced STAT1 hyperactivation, which upregulated SMAD7, an inhibitor of TGF-β signaling. FIST treatment also desensitized lymphocytes to TGF-β–mediated suppression and induced inflammatory cytokine production. In vivo, FIST-expressing B16 melanoma cells or PANC02 pancreatic cancer cells resisted tumor growth and demonstrated a potent bystander antitumor effect. FIST also caused recruitment of NK, NKT, B, and $CD8^+$ T cells to tumor sites and the production, via STAT1 activation, of high levels of the angiostatic chemokine CXCL10. Analysis of immunodeficient mice suggested a primary role for FIST-responsive NK cells in antitumor protection, and FIST stimulation of NK cells induced T-bet expression and promoted Th1 activity. The development

of FIST represents a strategy for tumor therapy that simultaneously targets angiogenesis and augments host antitumor activity.

## Catching Sight of Innate Defenses




Following eye surgery or trauma, *Staphylococcus aureus* can gain access to the retina and cause endophthalmitis. The mechanisms of antibacterial defense in this disease are not well understood but are presumed to involve retinal glial cells. Shamsuddin and Kumar (p. 7089) found that Muller glia, the most abundant type of glial cell in the retina, were activated to become reactive glial cells by intravitreal injection of *S. aureus* or the TLR2 ligand Pam3Cys. Treatment of Muller glia with Pam3Cys or *S. aureus* also induced the upregulation of TLR2 expression and stimulated signaling via NF-κB and MAPK pathways. These stimulated Muller glia produced the proinflammatory molecules IL-6, IL-8, TNF-α, and IL-1β in a TLR2 signaling-dependent fashion. In addition, the antimicrobial peptide LL-37 was upregulated in these cells following stimulation. Finally, conditioned media from Muller glia treated with Pam3Cys or *S. aureus* (either live or heat-killed) exhibited strong bactericidal activity. Muller glial cells in the retina can therefore play a role in innate antimicrobial defense through recognition of invading pathogens via TLR2, leading to the production of inflammatory mediators and induction of direct antibacterial activity.

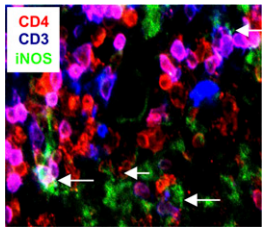
## Lupus's Cycle of Susceptibility

In murine models of lupus, B1a cells are overrepresented, especially in the peritoneal cavity, but their role in lupus pathogenesis remains poorly defined. B1a cells are known to bear an autoreactive repertoire, and their expansion is associated with the *Sle2c1* lupus susceptibility locus. To determine the gene within this locus responsible for the expansion of the B1a compartment, Xu et al. (p. 6673) first used fine genetic mapping to narrow the *Sle2c1* genomic interval and then identified candidate genes through microarray analysis. The most promising candidate identified by this mechanism was *Cdkn2c,* which encodes the cyclin-dependent kinase inhibitor $p18^{INK4c}$. $p18^{INK4c}$ activity induces early G1 cell cycle arrest and is important for plasma cell differentiation. Accordingly, mice bearing the NZB (lupus-prone) allele of *Sle2c1* demonstrated impaired Ab responses following immunization, compared with mice bearing the wild-type C57BL/6 allele. Mice with the NZB allele also exhibited impaired plasma cell differentiation in splenic B cells and increased B1a cell proliferation relative to control mice. These observations were tied to a novel SNP, −74 C/T, in the *Cdkn2c* promoter whose T allele, present in NZB mice, was associated with reduced *Cdkn2c* transcription. Taken together, these data suggest that $p18^{INK4c}$ regulates B1a cell homeostasis, and a reduction in its expression allows expansion of these potentially autoreactive cells.

## SARS Survivor Story

Severe acute respiratory syndrome (SARS) results from infection with the SARS-related coronavirus (SARS-CoV), which caused a global epidemic in 2003. An understanding of the long-term maintenance of immunity to SARS-CoV is necessary to effectively prepare for a re-emergence of this disease. Tang et al. (p. 7264) have analyzed the immune response to SARS-CoV in individuals 6 y after they recovered from infection with this virus. Pre-existing IgG Abs to SARS-CoV were undetectable in 21 of the 23 individuals, and the 2 remaining individuals had only low levels of Ab. Although B cells from the recovered SARS patients demonstrated similar responses to a SARS-unrelated Ag as did cells from controls, no SARS-CoV–specific memory B cell responses were detected in PBMCs from any of these individuals. In contrast, 60.8% of the recovered patients demonstrated SARS-CoV–specific memory T cell responses, whereas PBMCs from control individuals manifested no such response. Individuals who had developed severe clinical manifestations during infection had stronger memory T cell responses than did those who had been less ill. Thus, T cell memory is more effectively maintained long term than is B cell memory following infection with SARS-CoV. Expanding on this knowledge may have important implications for SARS vaccine development, as well as for the treatment of future SARS-CoV infections.

## Radical Redirection




TGF-β, in collaboration with other cytokines, can direct $CD4^+$ T cell differentiation toward the regulatory T (Treg), Th17, or Th9 cell phenotypes. NO is produced by a variety of immune cells and has also been suggested to modulate T cell differentiation, leading Lee et al. (p. 6972) to assess the effects of NO on TGF-β–regulated T cell polarization. In the presence of NO, TGF-β–induced Foxp3 induction and Treg differentiation were strongly inhibited, whereas T-bet induction and Th1 differentiation were promoted. Although NO and IL-6 both acted cooperatively with TGF-β, NO antagonized IL-6's Th17-promoting activity and diverted naive T cells toward the Th1 lineage. Addition of retinoic acid, however, dominated over both NO and IL-6, directing differentiation back toward the Treg lineage. Mechanistic analysis demonstrated that NO directly interacted with T cells and enhanced signaling through the IFN-γR, augmenting nuclear localization of STAT1 and expression of T-bet. Investigation of the effects of physiologically produced NO on T cell differentiation revealed that, during infection with *Listeria*, the TNF and inducible NO synthase-producing dendritic cell (DC) subset could form clusters with conventional DCs and T cells and promote Th1 differentiation. These data define contributions of the free radical environment to the finely tuned control of T helper cell differentiation.

**Summaries written by Jennifer Hartt Meyers Ph.D.**