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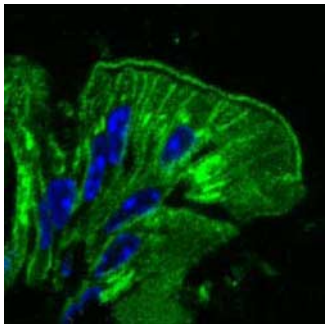
THE JOURNAL OF IMMUNOLOGY

In This Issue

Annexin Makes It Better



Annexin A1 (AnxA1) is an anti-inflammatory protein that has been shown to have a protective effect in various models of inflammation and inhibits lymphocyte migration and activation. As AnxA1 is secreted during inflammation of the intestinal mucosa, Babbin et al. (p. 5035) investigated whether this phospholipid-binding protein plays a role in protecting mice from colitis and in their recovery from intestinal pathogenesis. Mice treated with dextran sulfate sodium (DSS) to induce colitis displayed increased amounts of AnxA1 expression in the epithelia of the colonic mucosa. AnxA1-deficient animals were more susceptible to DSS-induced colitis than wild-type mice with increased pathogenesis and intestinal neutrophilic infiltrate. Compared with wild-type animals, recovery of AnxA1$^{-/-}$ mice was impaired after removal of DSS treatment and this effect was independent of inflammatory cell infiltration of the mucosa. This led the authors to test whether AnxA1 was exerting its protective effects on the colonic mucosa through the formyl peptide receptor-like 1 (ALK/FPRL-1). Treatment with aspirin-triggered lipoxin A4 (15-epi-lipoxin A4), an ALK/FPRL-1 agonist, mimicked the effect of AnxA1 in DSS-induced colitis, rescuing AnxA1$^{-/-}$ animals from their enhanced sensitivity. 15-Epi-lipoxin A4 showed little protective effect in DSS-treated wild-type mice. Thus, endogenous AnxA1 protects the colonic mucosa against DSS-induced inflammation through an ALK/FPRL-1-dependent mechanism.

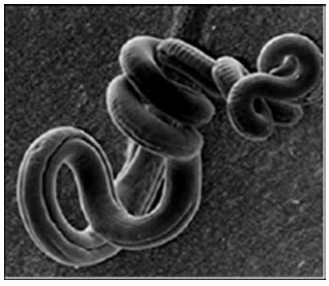
Long-Term Tolerance

Dendritic cells (DCs), with their ability to present Ag and modulate immune responses, make attractive immunotherapeutic targets. However, manipulation of DCs ex vivo has presented various technical difficulties. To overcome these difficulties, Dresch et al. (p. 4495) took an in vivo approach by designing an Ag-expressing, DC-specific self-inactivation (SIN) lentiviral vector. To restrict lentiviral expression of OVA to DCs, they used the 5′-untranslated region of the DC-specific transmembrane protein (DC-STAMP) gene as a promoter. Bone marrow from OT-II Ly5.2$^+$ mice was virally transduced with the DC-STAMP-OVA-expressing virus and transferred to irradiated Ly5.1$^+$ recipients to generate chimeric animals. The lentiviral expression of OVA in these animals was sufficient to cause a reduction in CD8$^-$CD4$^+$ thymocytes and a substantial deletion of CD4$^+$ OT-II T cells, leading to CD4$^+$ T cell tolerance. To test whether CD8$^+$ T cell tolerance could be also generated with this method, chimeras were created from bone marrow of OT-I mice transduced by the DC-STAMP-OVA virus in irradiated recipient animals. Once again, there were reduced numbers of thymocytes, this time CD8$^+$, and an overall reduction in the absolute number of OT-I T cells when compared with chimeras created with an OVA-deficient vector. CD8$^+$ T cell tolerance to OVA was generated and could not be broken with immunization. Tolerant CD8$^+$ T cells were not able to induce diabetes in a model of murine autoimmunity, and T cell responses to other Ags, such as HSV glycoprotein B, were not affected. These data show that Ag-specific T cell tolerance can be generated in vivo by lentiviral targeting of DCs and have potentially opened the door to manipulation of DCs in vivo.

The Next Generation of Celebrex?

Osteoarthritis (OA) patients have increased levels of PGE_2 in their synovial fluid and cartilage, but how this prostaglandin contributes to disease pathogenesis has remained unclear. Attur et al. (p. 5082) have elucidated the metabolic mechanism of PGE_2-mediated pathogenesis in cartilage. Using OA cartilage explants, the authors demonstrated that PGE_2 inhibited proteoglycan synthesis and increased collagen degradation; these effects could be inhibited with ilomastat, a matrix metalloprotease (MMP) inhibitor. In addition, PGE_2 was found to increase IL-1-induced MMP-13 secretion in OA explants while suppressing the secretion of MMP-1. Both of these effects could be reversed by treatment with the COX-2 inhibitor celecoxib (Celebrex). Celecoxib also inhibited the PGE_2 augmentation of IL-1-induction of aggrecanase 5 (ADAMTS-5), a molecule notable for its ability to cleave the cartilage component aggrecan. Quantitative analysis revealed that the PGE receptor 4 (EP4) was up-regulated in the cartilage of OA patients and that the use of the EP4 antagonist AH23848 replicated the celecoxib-induced inhibition of MMP-13 and ADAMTS-5 and the collagen degradation effects of PGE_2. Thus, the data elucidate an EP4-dependent mechanism for PGE_2 modulation of cartilage degradation and provide a novel therapeutic target that is more specific than that of celecoxib.

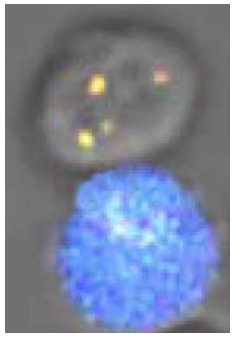
Resistin' Worms



Resistin-like molecule β (RELMβ) is secreted by goblet cells and is highly expressed in cystic fibrosis, inflammatory bowel disease, and helminthic infections. RELMβ belongs to the resistin-like family of small cysteine-rich molecules and has been shown to play a role in intestinal inflammation. Nair et al. (p. 4709) tested the role of RELMβ in both acute and chronic infection with the helminthic parasite *Trichuris muris*. With high dose or acute *Trichuris* infection, RELMβ was not necessary for generating the protective Th2 response that causes

parasite expulsion. However, low dose infection with *Trichuris* caused wild-type C57BL/6 mice to develop chronic infections with high levels of $CD4^+$ T cell-expressed IFN-γ and inflammation at the site of parasite infection. When RELM$\beta^{-/-}$ animals were given a low dose of the parasite, there was reduced expression of IFN-γ and TNF-α in parasite-specific $CD4^+$ T cells, no discernible intestinal inflammation, and no development of persistent infection. In vitro experiments with recombinant RELMβ caused macrophage activation as measured by MHCII expression and IL-12/23p40 expression, as well as macrophage-elicited secretion of IFN-γ by parasite-specific $CD4^+$ T cells. Thus, RELMβ plays a role in maintaining chronic parasite infections by promoting Th1 $CD4^+$ T cell responses through goblet cell-macrophage cross-talk.

Location, Location, Location



The mechanism by which lytic granules exocytose from $CD8^+$ cytotoxic lymphocytes is poorly understood. However, Ma et al. (p. 4716) have gone a long way toward showing that protein kinase C δ (PKCδ) plays an important role in this kinetic process. Having previously demonstrated that PKCδ regulates TCR-induced lytic granule polarization selectively in $CD8^+$ T cells, in this study the authors demonstrate that PKCδ localizes to the secretory lysosomes. During the process of target cell killing, PKCδ moved to the immunological synapse with the target cell, a journey that is vividly documented in the video accompanying the manuscript in supplemental material. Mechanistic studies demonstrated that TCR ligation caused rapid phosphorylation of PKCδ at the site of the activation loop. In addition, granule exocytosis was shown to be kinase dependent, as PKCδ mutants deficient in kinase activity were unable to regulate exocytosis. By looking at where PKCδ localized within the $CD8^+$ CTL and following the molecule's movements in living cells, the authors have demonstrated that PKCδ is responsible for translating TCR signals into polarized granule secretion.

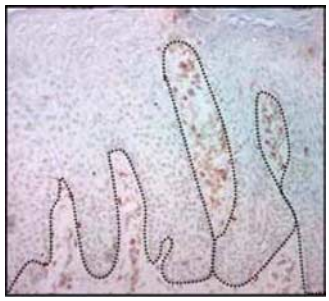
Patterns of Uveitis

Autoimmune uveitis is a T cell-mediated, intraocular disease characterized by inflammation. Unfortunately, autoimmune uveitis is very heterogenic, both in its clinical aspects and in the autoantigens that trigger disease, making treatment of disease difficult. Li et al. (p. 5147) have attempted to find a consistent pattern among uveitis patients by looking at the gene expression profile of 50 patients with noninfectious uveitis syndrome. Sixty-seven inflammation- and autoimmunity-associated genes were identified. Some of the genes that were increased in patients compared with normal individuals included *IL-22*, *IL-19*, *IL-20*, and *IL-25/IL-17E*. Microarray analysis showed distinctive expression patterns associated with clinical activity and quiescence and showed concordance between the expression profiles of siblings with similar clinical manifestations of disease. Expression of the IL-10 family member IL-22 was substantially increased in uveitis patients with variability among individuals. IL-22 was shown to induce apoptosis in primary retinal pigment cells, potentially by decreasing the level of phosphorylated Bad. These data provide evidence that a number of IL-10 family cytokine genes are implicated in autoimmune uveitis and that IL-22 can have a direct effect on human retinal epithelia.

The Making of an Eosinophil

The hematopoietic transcription factor IFN consensus binding protein (Icsbp), also known as IFN response factor-8 (Irf8), has several functions in myelopoiesis and host defense. Icsbp$^{-/-}$ mice develop a myeloproliferative syndrome and decreased resistance to viral, parasitic, and intracellular bacteria infection. Milanovic et al. (p. 5045) used Icsbp$^{-/-}$ mice to determine the role of this transcription factor in eosinophil development. Loss of Icsbp resulted in an 8-fold reduction in the number of bone marrow eosinophils compared with the bone marrow of wild-type mice. Peritoneal eosinophils, both those occurring normally in the peritoneal cavity and after thioglycollate induction, were reduced in Icsbp$^{-/-}$ mice. Upon challenge of Icsbp$^{-/-}$ mice with *Nippostrongylus brasiliensis*, a parasitic nematode known for its ability to elicit an eosinophilic response, there was no eosinophilia despite the presence of a strong IL-5 response. Eosinophil progenitors (EoP) were also reduced and those that were present had an impaired ability to differentiate. *Gata1* expression was reduced in EoPs and mature eosinophils of Icsbp$^{-/-}$ mice. Thus, the transcription factors Icsbp and Gata1 were determined to be acting in concert to direct the differentiation program of eosinophils.

Th17 T Cells, Brought to You by IFN-γ



In some pathogenic conditions, Th1 and Th17 T cells colocalize. This has presented investigators with a paradox, as in vitro IFN-γ from Th1 cells has been shown to suppress Th17 cell development. Now, in experiments investigating human psoriasis lesions, Kryczek et al. (p. 4733) have challenged the idea of Th1-mediated Th17 suppression. Within psoriatic skin lesions they found increased numbers of both $CD4^+IL\text{-}17^+$ and $CD8^+IL\text{-}17^+$ T cells. Myeloid APCs were demonstrated to be important for the increased cell number. Blood and skin samples from psoriatic patients had increased numbers of Th1 cells and increased levels of IFN-γ, the cytokine responsible for programming myeloid APCs to secrete IL-1 and IL-23. This, in turn, caused the induction of $IL\text{-}17^+$ T cells. In addition, IFN-γ was shown to be essential for stimulating APC production of the chemokine CCL20, causing migration of $IL\text{-}17^+$ T cells. Secretion of IL-17 from T cells in psoriatic lesions caused the surrounding keratinocytes to secrete the antimicrobial and chemotactic molecule β-defensin 2. Taken together, the data support the idea that instead of suppressing Th17 development, Th1 cells are taking an active part in inducing and attracting IL-17-expressing cells, leading to a collaborative effect in autoimmunity.

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