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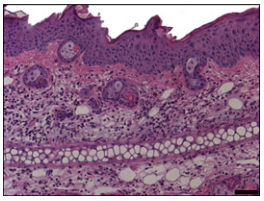
Basophils Inflame ILC2s in Skin



Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by recruitment of innate immune cells, IgE induction, and robust production of type 2 cytokines IL-4, IL-13, and IL-5. Basophils and group 2 innate-like lymphoid cells (ILC2s) contribute to type 2 cytokine-mediated immunity in a thymic stromal lymphopoietin–dependent manner in AD; however, whether these two cell types interact in these responses is unknown. To explore this possibility, Kim et al. (p. 3717) analyzed skin punch biopsies from AD patients and healthy controls and found accumulation and colocalization of ILC2s and basophils in AD skin lesions but not control skin. To determine the temporal kinetics and relative roles of basophils and ILC2s in AD skin, an AD-like state was induced in *Rag*$^{-/-}$ mice using topical treatment of the vitamin D analog MC903. Basophils accumulated in inflamed skin earlier than ILC2s, suggesting that basophil responses preceded ILC2 responses. Because basophils are thought to promote skin inflammation by production of IL-4, the authors assessed whether this cytokine could play a role in ILC2 responses and found that ILC2s expressed IL-4Rα and proliferated in an IL-4–dependent manner. *Il-4*$^{-/-}$ basophil transfer to wild-type mice induced basophil, but not ILC2, accumulation in the skin, suggesting that ILC2 responses in inflamed skin were dependent on basophil-derived IL-4. Collectively, these results indicate that ILC2 responses in cutaneous inflammation are regulated by basophil-derived IL-4.

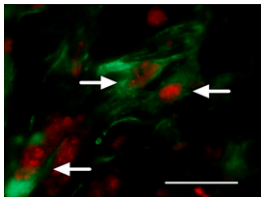
Cis-Elements Wrangle Vκ Ab Genes

V(D)J recombination is a primary means of generating diversity in the Ab repertoire; however, the mechanistic details behind this process have not been fully elucidated. Previously, deletion of DNase I hypersensitive sites (HSs) found in the Vκ–Jκ intervening region revealed that HS1-2 (Cer) play roles in locus contraction and HS3-6 (Sis) are important in generation of Ab diversity. In this issue, Xiang et al. (p. 3746) examined HS1-6$^{-/-}$ mice lacking all six HSs to seek out previously unknown functions for these *cis* elements in Vκ gene rearrangements. They found similar overall levels of L chain isotype exclusion, allelic exclusion, and Vκ gene recombination in these mice relative to wild-type mice. Cloning and sequencing Vκ–Jκ1 rearrangement products from HS1-6$^{-/-}$ pre-B cells revealed dramatically enhanced Jκ proximal Vκ gene usage (~ 95%) compared with WT cells (~ 10%). Fluorescence in situ hybridization analyses revealed that excessive proximal Vκ gene usage may be a result of defects in Igκ locus contraction. Notably, both pre-B and splenic B cells exhibited a pronounced increase in unrearranged proximal Vκ gene transcripts that was not previously observed in Cer or Sis deletion mutants. Together, these data indicate that the complete HS1-6 deletion encompassed not only regulatory mechanisms for Vκ gene rearrangement found in previous HS deletion studies, but also an additional role for this region in silencing transcription of germline proximal Vκ genes.

Th2 Cells Trump Trematodes

Schistosomiasis is a parasitic disease that causes severe pathology in the intestine and liver of the host. Egg production by the trematode *Schistosoma mansoni* in the host elicits immune responses that involve production of the Th2-associated cytokines IL-4 and IL-13, which are integral to host survival; however, the primary effector cell producing these cytokines has yet to be clearly identified. To provide insight into this problem, Schwartz et al. (p. 3590) infected mice harboring a CD4$^+$ T cell–specific deletion of IL-4/IL-13 genes (4-13Tko) or mice that entirely lacked IL-4/IL-13 (4-13ko) and found that CD4$^+$ T cell production of these cytokines was required for large granuloma formation, recruitment to granulomas of alternatively activated macrophages (required to prevent fatal outcomes in *S. mansoni* infection), and survival of infected mice. Mice with a basophil-specific deletion of IL-4/IL-13 had wild-type (WT)-like responses to *S. mansoni* infection, indicating that production of these cytokines by basophils was dispensable. T cells from 4-13Tko and 4-13ko mice infected with *S. mansoni* exhibited defective Th2 responses, producing increased levels of the Th1 cytokines IFN-γ and TNF-α. The Th2 Ab response to *S. mansoni* infection was also impaired in 4-13Tko and 4-13ko mice. Together, these data indicate that CD4$^+$ T cells, but not innate immune cells, are a primary source of IL-4/IL-13 cytokines that are vital to resolving *S. mansoni* infection.

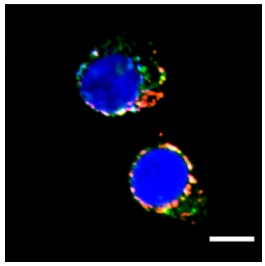
Soluble IL-6R Fires up Fibrosis



Idiopathic pulmonary fibrosis (IPF) is a poorly understood lung condition characterized by chronic fibrosis of lung tissue, respiratory failure, and death. Previous studies have shown that IL-6 levels are elevated in humans and mice with pulmonary fibrosis. Le et al. (p. 3755) now show that IL-6 *trans* signaling driven by soluble (s) IL-6Rα is critical to the development and progression of fibrosis in a mouse model of pulmonary fibrosis. Levels of sIL-6Rα were elevated in lung tissue from IPF patients and in the lungs of mice with chronic pulmonary fibrosis caused by i.p. bleomycin (IPB) treatment. Expression of a disintegrin and metalloprotease (ADAM) 17, known to cause shedding of sIL-6Rα by cleavage of membrane-bound IL-6Rα, was elevated in IPB-treated mice and was associated with heightened sIL-6Rα levels

and an increase in the number of alveolar macrophages in fibrotic lung tissue. Moreover, ADAM17 was shown to promote shedding of membrane-bound IL-6Rα in activated macrophages. Treatment of IPB mice with gp130Fc, a selective inhibitor of IL-6 *trans* signaling, significantly reduced levels of sIL-6Rα in the lungs. Interestingly, gp130Fc treatment was also associated with attenuated pulmonary fibrosis, including decreased myofibroblast levels and reduced fibronectin and collagen production. Together, these results indicate that IL-6 *trans* signaling plays a vital role in the pathogenesis of pulmonary fibrosis and may provide a new avenue for IPF treatment.

Chasing HIV out



Antiretroviral drug therapies have decreased HIV-1–related morbidity and mortality, but have not led to complete clearance of virus infection because of long-lived latently infected cells. Despite evident anti–HIV-1 Ab responses in patients, virions and infected cells evade Ab-dependent complement-mediated lysis (ADCML) via surface expression of regulators of complement activation (RCA). Here, Lan et al. (p. 3577) used a two-pronged approach that combined proviral stimulation and administration of an RCA blocker to eradicate cells latently infected with HIV-1. In a human T cell line latently infected with HIV-1 (ACH-2 cells), prostatin and histone deacetylase inhibitors, particularly romedepsin, stimulated virion production and expression of viral proteins such as HIV-1 Env. Proviral stimulant activity was unaffected by antiretroviral protease inhibitors such as atazanavir and darunavir and the reverse transcriptase inhibitor emtricitabine. Further, HIV-1 Env was found to colocalize with CD59 (an RCA that regulates membrane attack complex formation during complement activation) in lipid rafts of provirus-activated cells. This colocalization suggests that a viral protein and an RCA element directly interact on the cell surface. Importantly, both provirus-activated primary $CD4^+$ T cells and ACH-2 cells exposed to an RCA blocker (BRIC229) and polyclonal anti–HIV-1 Abs or plasma from infected patients were sensitive to ADCML. Taken together, these results reveal a method for directly targeting latent HIV-1 reservoirs that may assist in overcoming a significant hurdle to resolving HIV-1 infection.

C5a Complements Th17 Cells in SLE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by high systemic levels of type-1 IFN and the generation of anti-nuclear Abs and glomerulonephritis. Somewhat paradoxically, Th17 cells have also recently been implicated in SLE pathology, although differentiation of this subset is normally inhibited by type-1 IFN–induced pathways, including the induction of IL-27 secretion by macrophages. To address this conundrum, Pawaria et al. (p. 3288) explored the impact of C5aR signaling, which has been shown to block type-1 IFN–mediated production of IL-27 in murine macrophages, on generation of Th17 cells in SLE. Bone marrow–derived macrophages (BMDMs) treated with IFN-α and C5a expressed lower IL-27 levels than BMDMs cultured with IFN-α alone. Significantly fewer $CD4^+$ T cells differentiated into Th17 cells when treated with supernatant from BMDMs cultured with IFN-α versus supernatant from BMDMs treated with IFN-α and C5a. Fewer Th17 cells, along with decreased disease incidence, were also found in C5aR-deficient mice compared with wild-type mice in a pristane-induced lupus model, providing in vivo evidence that C5a plays a role in Th17 cell development. In humans, relative to serum from healthy controls, serum from SLE patients exhibited higher levels of the C5a cleavage product C5adesArg, which directly correlated with an increase in the percentage of Th17 cells in SLE patient blood. These data suggest that C5a may have a causative role in the generation of Th17 cells in SLE and could represent a novel therapeutic target for treatment of this disease.

GATA Be a T Cell

Gata3 expression is integral to T cell development, but germline deletion of this gene causes embryonic lethality prior to T cell precursor development in the fetal liver, which complicates detailed studies of *Gata3* in T cell development. To circumvent this difficulty, Scripture-Adams et al. (p. 3470) used a *Gata3*-specific shRNA retroviral construct (G3-3W) to transduce cultured fetal liver precursors (FLPs) or double negative (DN) T cells (derived from fetal liver cultures) at specific stages of T cell development. Transduced FLPs cultured under T cell–promoting conditions expressed 50% less GATA-3 protein compared with untransduced cells and exhibited impaired proliferation and viability, as well as a developmental block at the DN2 to DN3 transition. G3-3W-transduced FLPs that reached DN1-, DN2a-, and DN2b-like phenotypic stages exhibited increased expression levels of *Spi1* (PU.1) and *Bcl11a* (genes that promote commitment to B cell and myeloid lineages, respectively) and reduced levels of *Bcl11b* and *Ets1* (genes that promote T cell development). To tease out more transient and subtle gene expression changes, the authors used retroviral Cre transduction of cells from mice expressing a floxed *Gata3* cassette to acutely delete GATA-3 at different DN stages and, from genome-wide analyses of sorted DN populations, found that GATA-3–deficient DN2 cells exhibited changes in several genes known to regulate lineage commitment. In further studies, dose-dependent GATA-3 expression potently affected commitment to T cell, B cell, and myeloid cell lineages. These data indicate that the timing, dosage, and duration of GATA-3 expression have profound regulatory consequences on the development of T cells and other immune cell lineages.