

In This Issue

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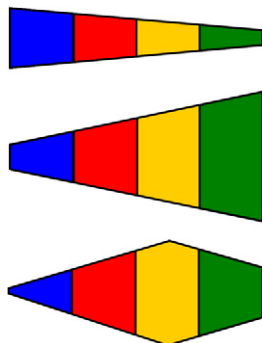
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Jogging T Cell Memory

T cell differentiation is associated with changes in cell trafficking, suggesting that different functional subsets might express specific homing receptors. In support of this idea, central and effector memory T cell subsets were identified based on expression of the chemokine receptor CCR7. Zhang et al. (p. 6646) have characterized additional subsets of human CD4⁺ CD45RO⁺ effector/memory T cells based on their expression of CCR2 and CCR5. The authors propose that CD4⁺ T cells undergo sequential differentiation from CCR5⁻CCR2⁻ to CCR5⁺CCR2⁻ to CCR5⁺CCR2⁺ surface phenotypes independently of CCR7 expression. Differentiation along this pathway was found to involve progressive increases in memory characteristics, effector activities (both in speed of activation and quantity of cytokine production), and responsiveness to IL-7. The CCR5⁺CCR2⁻ subset was enriched for regulatory T cells and activated/proliferating cells and, of the subsets, was most susceptible to cell death. Compared with the other subsets, the CCR5⁺CCR2⁺ cells demonstrated the greatest proliferative response to tetanus toxoid and responded to the broadest array of chemokines. The characteristics of this CCR5⁺CCR2⁺CD4⁺ memory T cell subset suggest that these cells may be poised for rapid effector responses, and the generation of these cells may be a useful goal of vaccine development.



Committing to a B Cell Future

Commitment of hematopoietic progenitor cells to the B cell lineage requires the actions of a complex network of genetic factors, including the transcription factors E2A, EBF, and Pax5, which act sequentially and synergistically to coordinate early B cell differentiation. Gwin et al. (p. 6572) compared the gene expression profiles of EBF^{-/-} and Pax5^{-/-} cell lines in hopes of identifying novel events involved in B lineage specification. A cluster of homeobox (*hoxa*) genes, especially *hoxa9*, was strikingly upregulated in EBF^{-/-} compared with Pax5^{-/-} cells. Further analysis demonstrated that *hoxa9* transcription was developmentally regulated along with *flt3*, and the downregulation of both genes corresponded with EBF induction and B cell fate commitment. *Flt3* is important for the maintenance of lymphoid progenitor cells, and *Hoxa9* was found to directly regulate *flt3* expression in vivo. Mice lacking *hoxa9* demonstrated impaired production of B cell precursors, indicating

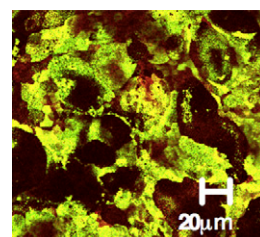
the importance of *Hoxa9*-mediated *Flt3* regulation in B cell development. Although the expression of EBF inversely correlated with that of *Hoxa9*, EBF did not directly regulate the *hoxa9* gene. Through its identification of a homeobox gene, this study provides important developmental insight into the role of these critical genes in the regulation of B cell lineage commitment.

Blk Branches Out

Functional differences between $\alpha\beta$ and $\gamma\delta$ T cells could stem from differences in signaling pathways downstream of the $\alpha\beta$ and $\gamma\delta$ TCRs. Through transcriptional profiling of mature $\alpha\beta$ and $\gamma\delta$ T cells, Laird et al. (p. 6518) found that the gene encoding the Src family kinase B lymphoid kinase (Blk), which was thought to be B cell specific, was expressed in $\gamma\delta$ but not $\alpha\beta$ T cells. However, Blk was present in only a subset of $\gamma\delta$ T cells and was therefore an unlikely candidate for general $\gamma\delta$ TCR signaling. Blk was also expressed in double negative thymocytes, and although not required for $\gamma\delta$ T cell lineage commitment, it was upregulated in $\gamma\delta$ thymocytes and downregulated in $\alpha\beta$ thymocytes following the $\alpha\beta/\gamma\delta$ lineage decision. Cell-intrinsic defects in immature double negative thymocyte proliferation and in regulation of progenitor cell frequencies in mice lacking Blk further demonstrated the importance of this kinase in early thymic development. Interestingly, Blk was preferentially expressed in IL-17-producing $\gamma\delta$ T cells and was required for their development. Blk expression is therefore not limited to B cells but is also important for T cell development. Furthermore, these results provide important insight into the molecular regulation of the differentiation and maintenance of the IL-17-producing subset of $\gamma\delta$ T cells.

Setting Neutrophils Free

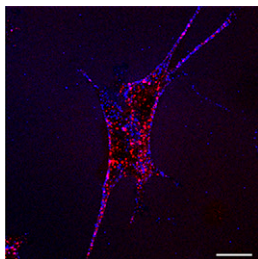
The migration of polymorphonuclear leukocytes (PMNs) across the intestinal epithelium concludes with their release from the luminal epithelial surface. To identify proteins that participate in this process, Brazil et al. (p. 7026) generated a panel of mAbs against IFN- γ -treated epithelial cells and analyzed their effects on PMN transepithelial migration. This screen identified an Ab, dubbed GM35, that specifically enhanced PMN adhesion to the apical epithelial surface in vitro. The protein Ag recognized by GM35 was induced by IFN- γ and expressed on the apical membranes of cells in the inflamed human colonic epithelium. This Ag was identified as the highly glycosylated CD44 splice variant CD44v6. During PMN transepithelial migration, a soluble form of CD44v6 was released, and this release was prevented by treatment with GM35. These data suggest that the release of soluble CD44v6



regulates PMN detachment from the apical epithelial surface of the intestinal lumen and thus plays a role in PMN clearance during inflammation. CD44v6 has been shown to be upregulated in human inflammatory bowel diseases, and this demonstration of its role in PMN transepithelial migration may therefore have therapeutic relevance.

To Bind or Not To Bind?

The heat shock protein GRP94 acts both in innate immunity through TLR2 and TLR4 activation and in adaptive immunity by guiding antigenic peptides into the cross-presentation pathway. CD91 was identified as an endocytic receptor for GRP94, but this designation has become controversial. Jockheck-Clark et al. (p. 6819) sought to determine definitively whether CD91 indeed plays a role in GRP94-mediated cross-presentation. Analysis of CD91-deficient cell lines and cells treated with CD91-directed small interfering RNAs indicated that binding of the GRP94 N-terminal domain (GRP94.NTD) was CD91 independent. Instead, the GRP94.NTD bound to cell surface heparan sulfate proteoglycans. CD91 also did not contribute to the cellular internalization of GRP94.NTD, which occurred with different kinetics and in different cellular locations than that of the CD91 ligand, receptor-associated protein (RAP). In addition, GRP94.NTD-mediated cross-presentation occurred via a non-receptor-mediated uptake pathway and was not competitively inhibited by CD91 ligands. By this demonstration that CD91 is not a receptor for GRP94, the authors may have finally resolved an important question that will force re-analysis of a great deal of data and may affect the development of human therapies.



CCL26, the Center of Attention

Members of the large family of chemokines interact with their receptors promiscuously and are classified by the position of two conserved N-terminal cysteine residues into CC, CXC, C, or CX3C subsets. Human CCL26 (eotaxin-3) was identified as a ligand for CCR3 and has been implicated in Th2-skewed disorders that involve eosinophilic infiltration. This chemokine, which has no mouse orthologue, also acts as an antagonist of CCR1, CCR2, and CCR5. In this issue, Nakayama et al. (p. 6472) demonstrate that CCL26 is not limited to interactions with CC chemokine receptors, but also specifically interacts with the Th1-associated receptor CX3CR1. In vitro, CCL26 induced calcium flux and chemotaxis in CX3CR1-transfected cells and also attracted CX3CR1-expressing NK cells, CD8⁺ T cells, and monocytes. Vascular endothelial cells produced CCL26 following treatment with the Th2 cytokine IL-4, leading to firm adhesion of CX3CR1-expressing cells, similar to the adhesion caused by Th1 cytokine-induced CX3CL1 production. Corresponding to its interaction with both CCR3 and CX3CR1, CCL26 could induce the migration of both eosinophils and NK cells in vivo. mRNA for CCL26 was found in skin lesions of

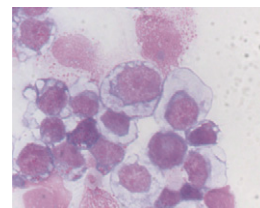
Th2-associated atopic dermatitis but not Th1-associated psoriasis. Thus, CCL26 may play a dual role in immunity by attracting both CCR3-expressing eosinophils and CX3CR1-expressing NK cells, CTLs, and monocytes.

IL-17 Battles the Bulge

Inflammatory mediators are involved in the link between obesity and metabolic dysfunction, and inflammatory T cell populations are known to accumulate in obese adipose tissue. Using a mouse model of obesity, Zúñiga et al. (p. 6947) sought to determine whether the upregulation of the proinflammatory cytokine IL-17 observed in obese patients influences metabolism and obesity or is simply a by-product of obesity-induced inflammation. IL-17-producing $\gamma\delta$ T cells were found in adipose tissue, and the frequency of these cells increased as inguinal adipose tissue accumulated in mice fed a high-fat diet. Interestingly, mice deficient in IL-17 were more susceptible than wild-type mice to obesity, even when fed a low-fat diet. A mechanistic basis for this susceptibility was traced to IL-17's effects on adipocytes. IL-17 inhibited adipocyte differentiation in vitro, inhibiting lipid uptake and the expression of genes encoding cytokines, proadipogenic factors, and factors important for lipid and glucose metabolism. In mature adipocytes, IL-17 inhibited glucose uptake, and glucose metabolism was improved in young IL-17-deficient mice. Taken together, these data define a role for IL-17 produced by $\gamma\delta$ T cells in metabolic function and the development of obesity through the modulation of adipocyte differentiation and activity.

Impressionable NK Cells

Heterogeneity of the NK cell lineage is beginning to be appreciated, but it is not yet clear how cytokines might drive differentiation of these cells into different functional subsets. Brady et al. (p. 6679) assessed the consequences of treating NK cells with the inflammatory cytokines IL-4, IL-12, IL-15, IL-18, and IL-21. IL-4, IL-12, IL-18, and IL-21 each antagonized IL-15-induced NK cell proliferation and promoted cellular maturation. Different combinations of these cytokines induced distinct profiles of effector cytokine production, suggesting the development of NK cell effector subsets. A variety of synergistic and antagonistic relationships were also observed among the cytokines under investigation. Although IL-21 enhanced cytolytic capacity, all other cytokines analyzed suppressed NK cell cytotoxicity while promoting cytokine production and variations in cell surface phenotype. As one robust example of cytokine modulation of NK cell activity, IL-4 was shown to downregulate the expression of the activating receptor NKG2D both in vitro and in vivo. These data indicate that the cytokines present during an immune response can dramatically affect NK cell activity and suggest a plasticity of NK cell phenotype that may allow for rapid functional alterations in response to the cytokine milieu.



Summaries written by Jennifer Hartt Meyers, Ph.D.