

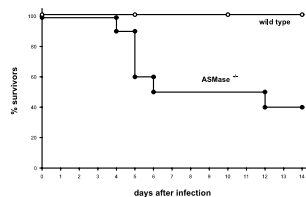
IN THIS ISSUE

Man and mouse KIR

Whereas NK cell receptors belonging to both the Ig-like (KIR) and C-type lectin families have been identified in humans, to date only receptors of the C-type lectin family have been detected in rodents. Hoelsbrekken et al. (p. 2259) have made an important new finding by isolating molecular clones of an Ig-like receptor (KIR3DL1) that is present in one copy in the rat genome and two copies in the mouse genome. The predicted sequences of the 55-kDa proteins are between 37.4% and 45.4% identical to primate KIRs and contain a pair of immunoreceptor tyrosine-based inhibition motifs in the cytoplasmic domains. Expression of KIR3DL1 appears to be restricted to NK cells in rodents. The authors' discovery expands opportunities for research into the functional role of KIRs by providing a readily accessible experimental animal model that had been lacking.

Not NO or ROI

Intracellular pathogens are sequestered and killed in the phago-lysosomal compartment of phagocytes during the early phase of the innate immune response. However, the mechanisms by which phagocytes exert their anti-bacterial effects are poorly understood. Utermöhlen et al. (p. 2621) investigated the role of acid sphingomyelinase (ASMase) in the host defense against *Listeria monocytogenes* infection. ASMase is found in the phago-lysosomal compartment, is activated by cytokines TNF- α and IFN- γ produced early in the infection cycle, and generates the signaling molecule ceramide. The authors found that ASMase^{-/-} mice are >100 times more susceptible to the lethal effects of *L. monocytogenes* than their wild-type counterparts. Although peritoneal macrophages from both wild-type and knockout mice produced nearly identical amounts of IL-1 β and IL-6, phagocytosed comparable levels of the bacteria and produced equal levels of reactive oxygen and nitrogen species, those from ASMase^{-/-} mice were deficient in killing the bacteria. It therefore appears that control of intracellular *L. monocytogenes* requires ASMase, but that ASMase does not control NO, ROI or cytokine secretion. The authors are investigating the possibility that ASMase is involved in killing bacteria within the phago-lysosome via a protease, perhaps cathepsin D, that is activated by ceramide.

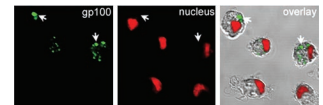


Memories

The Central and Effector Memory Hypothesis of Salusto and Lanzavecchia uses the expression of the CCR7 chemokine receptor to divide memory T cells into two phenotypic groups and to ascribe distinct functions to each of the two major subpopulations it defines. The hypothesis posits that CCR7⁺ cells ("central memory cells"), found in lymph nodes, are incapable of immediate effector functions and that CCR7⁻ cells ("effector memory cells") provide immediate effector functions, such as cytokine secretion and cytotoxicity. This scheme is challenged by Ravkov et al. (p. 2461) using a fluorescent tetramer of the CCR7 ligand, CCL19. The authors found that CCR7 expression levels discriminated between the memory CD8⁺ T cell population (CCR7^{int}) and the naive T cell population (CCR7^{high}). However, in a series of experiments with human CD8⁺ T cells from healthy donors, they found that both CCR7^{int} and CCR7⁻ cells expressed IFN- γ and TNF- α after short-term stimulation and both contained intracellular perforin before stimulation. Thus the Central and Effector Memory Hypothesis may need to be refined as further studies investigate the function of T cell groups defined by CCR7 expression.

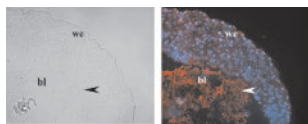
Nibbling

A widely held perception of dendritic cell function is that Ags are taken up only from cells killed by foreign pathogens or captured from neighboring apoptotic cells for presentation to T cells. However, the notion of "nibbling," or the acquisition of surface membrane Ags from live cells, is gaining ground as an explanation for the ability of dendritic cells to cross-present to T cells, as occurs in infections by noncytopathic viruses. Harshyne et al. (p. 2302) have established nibbling as a real phenomenon by examining pronase-sensitive surface receptors, one of which is the type A scavenger receptor (SR-A). Nibbling is highly efficient, with captured fluorescent-labeled membrane proteins accumulating in dendritic cell vesicles within three hours. Adenovirus-gp100, which localizes to the plasma membrane, was introduced into A549 tissue culture cells by virus infection. Addition of polyanionic SR ligands decreased dendritic cell uptake of gp100 from live and apoptotic cells, and Ab to SR-A decreased cross-presentation of gp100 by immature dendritic cells by 50%. The authors point out that SR-A receptor is not the sole mediator of nibbling since the SR-A Ab blocked cross-presentation only 50%. Other receptors, possibly of the SR family, might be involved.



Complementing eye (and limb) of newt

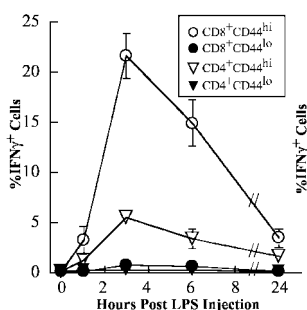
Evidence that members of the complement system have functions other than those involved in host defense and inflammation



has been accumulating slowly over the past several years. For example, complement component C3 is known to interact with proteins of the extracellular matrix, and mice lacking C5 lose the capacity to regenerate damaged livers. Capitalizing on the ability of a lower vertebrate, the newt, to regenerate body parts, Kimura et al. (p. 2331) have shown that C3 and C5 are differentially expressed during limb and lens regeneration. The authors developed C3- and C5-specific cDNA probes and Abs to follow expression of these components. C3 was found throughout limb regeneration, most prominently in the dedifferentiated blastema that is the source of new limb parts. In contrast, C5 was present in the wound epithelium that signals differentiated tissues to dedifferentiate in the first stage of regeneration. Similar patterns of expression were found in the regenerating eye. Neither C3 nor C5 was expressed in normal limb or eye. These findings raise the question of whether complement molecules play a role in pattern formation in the normal development of organisms.

Bystander activation

Interferon- γ plays an important role in innate and adaptive immune responses. The cells producing the cytokine are thought to vary according to the stage of infection, with NK or NKT cells being the source during the early Ag-independent phase and T cells during the later adaptive response. Kam-



bayashi et al. (p. 2399) questioned this assignment of roles and asked if other cell types are involved in the early stage. They measured IFN- γ production by memory (CD44^{high}) CD8⁺ T, NK, and NKT cells separated from spleens and draining lymph nodes of LPS-challenged mice. Memory, but not naive, CD8⁺ T cells represented 30% of the IFN- γ producing spleen cells and 70% of the IFN- γ producing lymph node cells. Cocultivation of the memory T cells with macrophages and dendritic cells from mice injected with LPS, poly I:C or type I IFN required exogenous IL-18 along with type I IFNs or IL-12 for maximum production of IFN- γ . Addition of IL-18 was not necessary if the dendritic cells were of bone marrow origin. These findings indicate that bystander activation by cytokines is sufficient to induce early IFN- γ production by memory CD8⁺ T cells in vivo, conferring on these cells an important role in innate immunity that is not dependent on previous exposure to the pathogen.

Antihistamine receptor

Atopic individuals have higher levels of Th2 cells and IgE and an increased susceptibility to viral infections due to lowered levels of released IFN- α . Mazzoni et al. (p. 2269) have traced these effects to the pattern of cytokines released by the interaction of histamine with plasmacytoid dendritic cells (pDC). Using exposure times as short as two hours, histamine suppressed release of IFN- α , TNF- α , and IL-2 from purified human pDCs stimulated by oligodeoxynucleotides or live flu virus. The action of histamine was mediated via the H2 receptor. Histamine also influenced the maturation of allogeneic naive T cells along the Th2 pathway. These findings offer the possibility that blocking H2 receptors on pDCs will enable atopic patients to more effectively fight viral infections.

How to escape proofreading?

A phenomenon termed kinetic proofreading has been set forth to explain the effect of rapidly dissociating ligands in reducing the delayed, more than the early, responses to aggregation of the IgE receptor Fc ϵ RI. One exception to kinetic proofreading is the transcription of the gene for monocyte chemoattractant protein-1 (MCP-1) where late transcription of the gene is enhanced, rather than reduced, by low doses of low affinity ligands. Eglite et al. (p. 2680) examined the role of Ca²⁺ as the component responsible for the aberrant response. Stimulated transcription of MCP-1 was diminished when receptor aggregation by low doses of Ags occurred in the presence of a calcium chelator, EGTA, or inhibitors of phospholipase C γ . The authors used a blocker of calcium influx to show that the Ca²⁺ was drawn from intracellular stores. Translation of the MCP-1 message did not require persistent aggregation of Fc ϵ RI. Thus, escape from the restraints of kinetic proofreading appears to occur via a soluble messenger, Ca²⁺, generated at a branch point in the receptor-mediated signaling cascade.

No bones about it

Monocyte chemoattractant protein-1 (MCP-1), produced by kidney mesangial cells, is an important mediator of inflammatory renal disease. Preventing the production or activity of the chemokine has been a goal of clinicians treating that disease. One path to reaching that goal may have been achieved by Lee et al. (p. 2557). The authors report that bone morphogenetic protein-7 (BMP-7), a member of the TGF- β superfamily expressed normally in developing and adult kidney, inhibited MCP-1 protein and mRNA syntheses in mesangial cells in culture. Both constitutive and IL-1 β -stimulated expression were reduced. BMP-7 also inhibited monocyte migration in Boyden assays. The inhibition of MCP-1 by BMP-7 appears to occur by suppressing phosphorylation of the 54-kDa c-Jun N-terminal kinase subunit after IL-1 β stimulation which in turn prevents AP-1 activation of the MCP-1 gene.

Summaries written by Dorothy L. Buchhagen, Ph.D.