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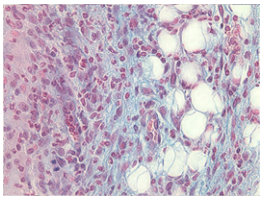
Lysosomes and Lyme Arthritis

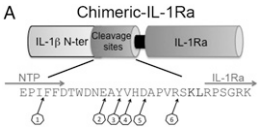


The lysosomal enzyme β-glucuronidase (GUSB) has been shown to be a key modulator of Lyme arthritis, a consequence of disseminated *Borrelia burgdorferi* infection. In this issue, Bramwell et al. (p. 1647) further investigated the role of GUSB in arthritis development by examining how GUSB deficiency affects lysosome function. Thioglycollate-treated peritoneal cells from C57BL/6 (B6) $Gusb^{Null}$ mice exhibited increased surface expression of the lysosomal membrane protein LAMP-1 compared with B6 and $Gusb^{Het}$ peritoneal cells, indicating a deficiency in lysosomal trafficking. Release of the lysosomal enzyme β-galactosidase and matrix metalloproteinase 9 (a known mediator of Lyme arthritis in mice) was measured in supernatants from *B. burgdorferi*–infected cells from B6 mice with hypomorphic *Gusb* activity (B6-$Gusb^{h}$) and found to be elevated when compared with supernatants from infected wild-type B6 cells, confirming enhanced lysosomal exocytosis. Following *B. burgdorferi* infection, B6-$Gusb^{h}$ mice developed moderate arthritis and deposits in their ankle joints of glycosaminoglycans, normally recycled in lysosomes. Rapamycin, which has previously been shown to suppress lysosomal exocytosis, was capable of inhibiting β-galactosidase release from *B. burgdorferi*-infected B6-$Gusb^{h}$ cells and reduced ankle swelling in vivo, despite increased bacterial burden. These observations were confirmed in the K/B x N model of murine arthritis. These results suggest that GUSB failure to regulate lysosomal trafficking leads to enhanced inflammation and immunopathology following inflammatory insults in arthritis, which can be ameliorated by rapamycin treatment.

HDAC3 Helps Teenage T Cells Mature

Newly generated T cells are functionally immature and these recent thymic emigrants (RTEs) are also susceptible to elimination through complement deposition. As histone deacetylase 3 (HDAC3) associates with NKAP, a transcriptional repressor previously shown to be crucial for T cell maturation, Hsu et al. (p. 1578) used conditional knockout (CD4-cre HDAC3 cKO) mice, in which HDAC3 is deleted at the double positive stage of T cell development in the thymus, to investigate whether HDAC3 is similarly required for postthymic T cell maturation. Although thymic development and egress of conventional T cells were normal, the pool of peripheral CD4 and CD8 T cells was decreased in CD4-cre HDAC3 cKO mice compared with wild-type mice, which was not due to a defect in homeostasis mediated by IL-7 signaling. To mark RTEs in vivo, CD4-cre HDAC3 cKO mice were crossed with Rag1-GFP reporter mice, which produce T cells that express GFP for 2–3 wk after thymic egress. In contrast to Rag1-GFP mice, most peripheral naive T cells in Rag1-GFP CD4-cre HDAC3 cKO mice were RTEs, although not all markers associated with T cell maturation were blocked. TNFα production from splenocytes stimulated with anti-CD3ε and anti-CD28 Ab in vitro showed that fewer mature naive T cells (MNTs) and RTEs from Rag1-GFP CD4-cre HDAC3 cKO mice were functionally licensed than cells from Rag1-GFP mice. Staining with Siglec-E, which binds α2,3 sialic acids and can indicate protection from complement targeting, was lower in MNTs lacking HDAC3. Supporting this, RTEs and MNTs from Rag1-GFP CD4-cre HDAC3 cKO mice had IgM, C1q, C3, and C4 on the cell surface, indicating that they were targets for elimination by the classical complement pathway. These results collectively demonstrate that HDAC3 is required for many facets of T cell maturation.

Incognito IL-1R Antagonist



The IL-1 family member IL-1Ra is an IL-1R antagonist that can serve to limit inflammation, and anakinra, a recombinant form of IL-1Ra, has been used to treat autoinflammatory diseases such as diabetes and gout. However, anakinra treatment results in systemic blockade of IL-1, increasing susceptibility to infection. Rider et al. (p. 1705) devised a constitutively inactive chimeric IL-1R antagonist designed to limit only local inflammation while sparing systemic IL-1 signaling. This IL-1Ra chimera was composed of the IL-1R binding site in IL-1Ra and the N-terminal peptide from IL-1β, whose binding to IL-1R requires prior activation through cleavage by serine proteases, such as those produced at sites of inflammation. Human lung adenocarcinoma (A549) cells pretreated with either IL-1Ra or the chimeric IL-1Ra were incubated with IL-1β, and IL-6 production was measured by ELISA. While IL-1Ra was able to block IL-1 activity and subsequent IL-6 production, cells treated with the chimeric IL-1Ra still produced IL-6. Incubation with neutrophil elastase, activated macrophages, activated human NK cells, or inflammatory cells from the peritoneum of polyethylene glycol-treated mice successfully cleaved the chimeric IL-1Ra, which was then able to block IL-1–induced IL-6 production by IL-1β–treated A549 cells. To determine in vivo efficacy of the IL-1Ra chimera, LPS and either anakinra or the chimeric IL-1Ra were mixed with Matrigel and plugs were implanted under the skin of mice. Compared with LPS alone, both anakinra and chimeric IL-1Ra were able to reduce the amount of cellular infiltration after 48 h. This chimeric IL1-Ra could potentially treat inflammatory conditions while mitigating some of the negative side effects observed with systemic IL-1R blockade.

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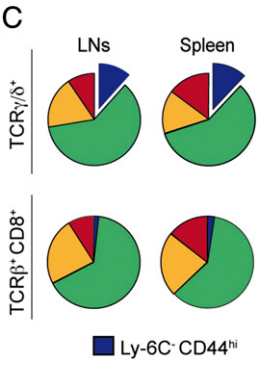
Gauging γδ T Cell Groupings

γδ T cells develop early during ontogeny and participate in both adaptive and innate immunity; however, the broad variety of potential ligands for these cells has complicated the study of their functions. In this issue, Lombes et al. (p. 1449) identified four subsets of mouse peripheral γδ T cells based on their expression of CD44 and Ly-6C. Three of these four subsets appeared to correspond to similar subsets of $CD8^+$ αβ T cells, but the Ly-$6C^-$ $CD44^{hi}$ subset appeared to derive from a separate lineage and corresponded to a previously identified population of $CD27^-$, IL-17–producing γδ T cells. The other three subsets produced IFN-γ and phenotypically resembled either effector/memory Ly-$6C^+$ $CD44^{hi}$ $CD8^+$ T cells or naive Ly-$6C^{-/+}$ $CD44^{lo}$ $CD8^+$ T cells. These three subsets responded to TCR stimulation but not TLR ligands, whereas the Ly-$6C^-$ $CD44^{hi}$ γδ T cell subset was hyporesponsive to TCR stimulation but could be stimulated by TLR ligands, suggesting a possible distinction between adaptive and innate immune functions among the cell subsets. The percentage of effector/memory-like Ly-$6C^+$ $CD44^{hi}$ γδ T cells increased with age, supporting their identification as potential memory cells. Although the two groups of $CD44^{hi}$ γδ T cells appeared to be terminally differentiated, the $CD44^{lo}$ subsets converted to a memory phenotype in lymphopenic conditions and could also be stimulated to differentiate into Th17-, Th1-, or iTreg-like cells. These data identify both innate and adaptive-like γδ T cells and suggest that the latter subsets share functional characteristics with $CD8^+$αβ T cells.



Helping T Cells Remember *Chlamydia*

Chlamydia trachomatis, the most common cause of bacterial genital tract infection, is rarely cleared by the host and does not induce protective $CD8^+$ T cell memory in humans or mice. In contrast, inoculating mice with a recombinant vaccinia virus expressing the *C. trachomatis* Ag CrpA (VacCrpA) yields robust $CD8^+$ T cell memory responses upon secondary Ag challenge. To provide insight into the disparity between these two immune responses, Zhang and Starnbach (p. 1665) conducted a side-by-side analysis of $CD8^+$ T cell responses in mice infected i.v. using these two pathogen models. They found both increased contraction of CrpA-specific $CD8^+$ T cells and poorer recall responses by these cells during secondary challenge in *C. trachomatis*–infected relative to VacCrpA-treated mice. The defects in $CD8^+$ memory T cell generation in *C. trachomatis*–infected animals did not result from impairments in IL-2R expression or in IL-2 responses in these cells. However, $CD8^+$ T cells from these mice more frequently expressed surface markers associated with a short-lived effector phenotype rather than a memory precursor phenotype early in the primary immune response. Ab depletion of IL-12 and IFN-γ, inflammatory cytokines expressed highly during *C. trachomatis* infection that could drive T cell differentiation toward a short-lived effector phenotype, boosted the number of CrpA-specific $CD8^+$ memory T cells recovered from *C. trachomatis*–infected mice and was also found to be beneficial for $CD8^+$ T cell primary and recall responses during mucosal *C. trachomatis* infection. Together, these data reveal new insights into the *C. trachomatis* $CD8^+$ T cell response and show that high levels of IL-12 and IFN-γ induced by infection with this pathogen are counterproductive for the development of effective $CD8^+$ T cell memory.

Hostile NK Cells Educate Themselves

Although NK cells are known to be central players in rejection of allogeneic cells in transplantation, the process of NK cell education in a prenatal transplant setting is relatively unexplored. Alhajjat et al. (p. 1506) performed in utero transplantation of BALB/c fetal liver cells into recipient C57BL/6 (B6) fetuses. Three weeks after birth, all B6 recipients with >1.8% BALB/c cells in the peripheral blood experienced long term tolerance and were termed engrafters; conversely, chimerism levels of <1.8% at this early time point eventually led to graft rejection. Ab depletion experiments confirmed that NK cells expressing Ly49D, which recognizes the MHC class I molecule $H\text{-}2D^d$ expressed by BALB/c cells, mediated rejection in this neonatal transplant model. Somewhat surprisingly, the frequency of $Ly49D^+$ NK cells in engrafter hosts was only slightly reduced compared with naive controls. These cells were further characterized to be mostly "friendly" NK cells, as they expressed compensatory inhibitory receptors. A remaining 4% of NK cells in engrafter hosts were dubbed "hostile" because they retained Ly49D expression but did not express these inhibitory receptors. Hostile $Ly49D^+$ NK cells were relatively immature and expressed lower levels of Ly49D compared with friendly $Ly49D^+$ NK cells, and were hyporesponsive to some forms of in vitro stimulation. The authors hypothesized that the higher frequency of friendly NK cells in engrafter mice may have been due to hostile NK cells converting to friendly NK cells in the periphery, which was confirmed with adoptive transfer experiments. These experiments also indicated that NK cell expression of compensatory inhibitory receptors was dependent on Ly49D recognition of alloantigen and the ability to do so was lost as the donor mice aged. These results unveil novel paradigms in allospecific education of developing NK cells.