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THE JOURNAL OF IMMUNOLOGY

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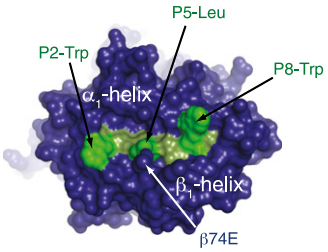
Naive Navigation



Recent advances in measuring the frequencies of different Ag-specific $CD4^+$ T cells in the naive repertoire have revealed that these populations can dramatically vary in size. Furthermore, the size of each naive population appears to directly affect the magnitude of the immune response. Chu et al. (p. 4705) used a peptide-MHC class II (pMHCII)-tetramer–based enrichment method to ascertain the influence of thymic selection and amino acid content of the antigenic peptide on naive $CD4^+$ T cell populations that specifically recognized two different I-A^b–binding peptides, which significantly varied in population size in naive mice. Mice with reduced negative selection showed less clonal deletion of precursors in the larger population compared with the smaller population. Even in the absence of negative selection, these two populations varied in size, suggesting other factors influenced naive $CD4^+$ T cell frequency. The presence of tryptophans in the antigenic peptide at the TCR contact residues P2 and P8 was associated with the larger naive T cell population as well. Further analysis will discern if preferential recognition of other amino acids by TCRs also influences naive population size. Overall, these findings present a new perspective of how both negative selection and the amino acid composition of antigenic peptides influence naive population size.

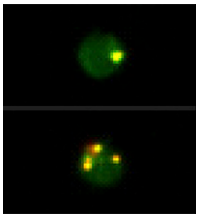
The Age Negotiator

Aging is associated with an accumulation of defects in T cell function that compromise adaptive immune responses against cancer and infection. Apoptosis is a key mechanism by which defective T cells are removed from the periphery. Tsukamoto et al. (p. 4535) show that decreased expression of the proapoptotic molecule Bim in $CD4^+$ T cells is associated with an increase in both the lifespan and emergence of T cell defects in aged mice. The effect of reduced Bim expression on $CD4^+$ T cell lifespan was confirmed through the generation of mixed bone marrow chimeras reconstituted with both $Bim^{+/+}$ and $Bim^{+/-}$ bone marrow cells. Naive $CD4^+$ $Bim^{+/-}$ T cells had a significantly greater lifespan in chimeric mice compared with $Bim^{+/+}$ T cells. Defects in Ag-specific proliferation, T cell help to B cells, and expression of senescence-associated genes increased in $Bim^{+/-}$ $CD4^+$ T cells in a manner dependent on both Bim expression levels and the advancing age of the chimeric mice. The emergence of these immunomodulatory defects appeared to require time spent in the periphery, as similar defects were not detected in newly generated $Bim^{+/-}$ $CD4^+$ T cells in aged mice. Taken together, these observations indicate that decreased Bim expression promotes the persistence of $CD4^+$ T cells and the concomitant accumulation of age-associated defects.

Targeting Granule Polarization

NK cell cytotoxicity is tightly controlled through engagement of inhibitory receptors. Nonetheless, the contribution of inhibitory receptor signaling to the blockade of cytotoxic granule polarization and degranulation is not clear. In this issue, Das and Long (p. 4698) show that inhibitory receptors are more effective at inhibiting granule polarization than degranulation. Human cell lines expressing the inhibitory receptor ligands HLA-C or HLA-E blocked granule polarization, release of granzyme B (a marker of degranulation), and CD16-driven MIP-1α secretion in NK cell clones expressing the HLA-matched inhibitory receptor. To refine these observations, the *Drosophila* cell line S2 was transfected with ICAM-1 in combination with HLA-C or HLA-E. This system revealed that only granule polarization, and not CD16-mediated release of granzyme B or MIP-1α, was hindered by inhibitory receptor engagement. These observations suggest that granule polarization can be inhibited by engagement of different inhibitory receptors, but degranulation is influenced by a variety of factors that may vary between cells. These findings also affirm that independent signaling events influence granule polarization and degranulation in NK cells.

C1q Curbs Lupus



Systemic lupus erythematosus (SLE) is an autoimmune disorder for which susceptibility is associated with multiple genetic factors, including deficiency in the complement component C1q. The mechanisms by which C1q deficiency provokes SLE are not clear. Santer et al. (p. 4738) show that C1q associates with SLE immune complexes (ICs) and promotes binding to monocytes instead of to plasmacytoid DCs (pDCs), which is associated with reduced IFN-α production. Disease severity in SLE patients correlates with elevated serum IFN-α thought to be produced by pDCs that endocytose SLE ICs. C1q was required to inhibit IFN-α production by SLE IC-stimulated PBMCs in vitro, as determined using a panel of human sera, including sera from SLE patients with known C1q deficiencies. Clinical observations confirmed that C1q-deficient SLE patients had elevated IFN-α serum levels, which correlated directly with Ro/SSA autoantibody levels. C1q affected SLE IC intracellular trafficking in monocytes such that C1q-bound SLE ICs were retained in early endosomes, but SLE ICs trafficked to lysosomes in the absence of C1q. These observations provide a unique perspective of

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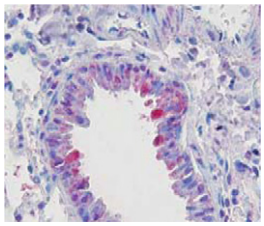
how C1q may protect against SLE and why C1q deficiency is associated with severe SLE.

Breathing Easier with NK Cells



Respiratory syncytial virus (RSV) causes an infection that can lead to severe bronchiolitis in infants and has been linked to childhood asthma. Recent clinical studies have shown an association between severe RSV infection in infants and an inadequate NK cell response. Using a murine model of RSV infection, Kaiko et al. (p. 4681) studied the role of NK cell depletion in a Th2-polarized response and allergic airway inflammation. Compared with NK cell-intact RSV-infected mice, mice depleted of NK cells produced less IFN-γ and generated RSV-specific Th2 responses following infection, and the RSV-specific Th2 polarization persisted during memory responses. In addition, exposure of NK cell-depleted mice to RSV in parallel with OVA, an innocuous bystander Ag, was associated with OVA-specific allergic airway inflammation. The Th2 response to RSV in NK cell-depleted mice required IL-25 production by airway epithelial cells, which promoted Th2 polarization by upregulating expression of the Notch ligand Jagged1 on dendritic cells. These results provide a potential mechanism that may explain the link between RSV-associated Th2 responses and the development of asthma and also highlight how an airway epithelium-associated cytokine can influence innate responses to infection.

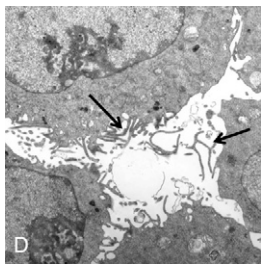
Crawling against the Flow

Adhesion molecules expressed on the surface of endothelial cells play a key role in orchestrating T cell extravasation from the bloodstream into inflamed tissues. Endothelial cells lining the vessels that form the blood–brain barrier are particularly impervious to transendothelial migration, and lymphocyte movement across this barrier is tightly regulated so as to limit inflammation in the CNS. Using knockout mice deficient in ICAM-1, ICAM-2, and VCAM-1, Steiner et al (p. 4846) assessed the contributions of these molecules in T cell extravasation through in vitro live cell imaging of T cell interactions with primary mouse brain microvascular endothelial cells. Endothelial ICAM-1 and VCAM-1 were both required to mediate shear-resistant T cell arrest under physiological flow conditions, but ICAM-2 had a more modest influence, which was undetectable in the presence of ICAM-1 and VCAM-1. Subsequently, T cell polarization and crawling, either with or against the direction of flow, required ICAM-1 and ICAM-2 but did not involve VCAM-1. In addition, live cell imaging confirmed that T cells predominantly crawled against the direction of flow prior to diapedesis. Overall, these results show that different adhesion molecules coordinate the various phases of T cell extravasation across the blood–brain barrier and serve as gatekeepers to the CNS.

Langerhans Cells Soothe Skin

A clear understanding of the role of Langerin-positive Langerhans cells (LCs) in the skin during adaptive immunity and contact hypersensitivity has been muddled by the presence of other Langerin-positive dendritic cell (DC) populations. Conflicting results over the contribution of LCs to contact hypersensitivity (CHS) have emerged from different transgenic mouse models in which DCs that expressed Langerin were inducibly or constitutively ablated by diphtheria toxin (DT). Bobr et al. (p. 4724) have developed a new transgenic mouse model in which human Langerin was expressed in conjunction with the diptheria toxin receptor (human Langerin-DTR) so as to restrict DT-mediated ablation to epidermal LCs. DT treatment of human Langerin-DTR mice effectively ablated LCs from the epidermis for up to 7 d posttreatment but did not affect murine Langerin-positive dendritic epidermal T cells or dermal DCs. Susceptibility of LC-deficient mice to CHS was assessed through cutaneous exposure to the hapten dinitrofluorobenzene 2 d after DT treatment followed by re-exposure 5 d later. DT-treated human Langerin-DTR mice developed a significant CHS response, but wild-type or untreated human Langerin-DTR mice showed no detectable CHS. Overall, results derived from this new mouse model indicate that LCs suppress CHS during the time of Ag exposure.

Microvilli Stymie Tumor Attack



The brain cancer glioblastoma multiforme (GBM) is one of the most lethal forms of cancer in humans, and its highly invasive nature makes it difficult to treat by conventional therapies. Hoa et al. (p. 4793) have evidence that suggests that GBM-associated gliomas are resistant to immune attack in part through the presence of cell surface-expressed microvilli. Microvilli were detected on the cell surface of several glioma cell lines and freshly isolated GBM neurosphere cultures through atomic force microscopy. The presence of microvilli-like structures on glioma cells was confirmed by confocal immunofluorescence and electron microscopy and was also seen in situ in intracranial gliomas, but similar structures were not detected on other cell types. Cytochalasin B treatment of gliomas disrupted the microvilli on the cell surface, indicating the presence of microfilaments within these structures. Detached glioma cells lacking microvilli were more susceptible to attack by lymphokine-activated killer cells, γδ T cells, or cytotoxic T cells in vitro compared with adherent glioma cells. Cytotoxic effector cell-mediated attack was ineffective despite the detection of perforin in microvilli that were resistant to killing, and microvilli that penetrated transwell chamber pores resisted the actions of cytotoxic effector cell and mechanical damage. These results provide a new perspective as to how microvilli protect GBM-associated glioma cells from immune attack.

Summaries written by Christiana N. Fogg, Ph.D.