Learning by immunity

The idea that the nervous system can affect the function of the immune system is well established; however, the influence that immunity has on behavior is only poorly understood. Now in the Journal of Experimental Medicine, Kipnis and colleagues demonstrate how CD4+ T cells serve an important role in learning and memory. Using the Morris water navigation task—a standard behavioral test—the authors show that CD4+ T cells expressing interleukin 4 (IL-4) are required for efficient learning and memory. Learning results in accumulation of CD4+ T cells in the meninges and, in the absence of IL-4, expression of proinflammatory molecules by meningeal myeloid cells. This observation is relevant since inflammation is known to impair neuronal function. Moreover, IL-4 is shown in vitro to elicit the production of brain-derived neurotrophic factor, a molecule known to be key to neuronal growth, learning and memory, by astrocytes. These findings might lead to new therapies for cognitive impairment. ZF J. Exp. Med. (5 May 2010) doi: 10.1084/jem.20091419

HIV evasion strategies

Autophagy is a self-digestion process involved in protein and organelle degradation that has emerged as a cell-autonomous defense mechanism against intracellular pathogens such as Mycobacterium tuberculosis and herpes simplex virus type 1. In Immunity, Piguet and colleagues show that HIV-1 infection inhibits autophagy in dendritic cells (DCs). Inhibition of autophagy impairs antigen presentation and Toll-like receptor signaling in DCs and increases viral spread to CD4+ T cells. These effects are dependent on interaction of the HIV-1 envelope protein with surface receptors, most probably CD4, and involve induction of the signaling mediator mTOR, a negative regulator of autophagy. Treatment with rapamycin, an mTOR inhibitor and autophagy inducer, leads to lower HIV-1 content in DCs and less transfer of HIV-1 from DCs to T cells. This could represent a novel method to mount efficient immune responses during early stages of infection. IV Immunity 32, 654–669 (2010)

Cytosolic trigger

Intracellular infection by the bacterial pathogen Listeria monocytogenes triggers the production of type I interferon. Cytosolic activation of interferon-regulatory factor 3 is necessary for this response, yet the microbial trigger that elicits this response remains unknown. In Science express, Woodward et al. identify the nucleotide metabolite cyclic diadenosine monophosphate (c-di-AMP) as the bioactive molecule responsible for inducing expression of interferon-β. L. monocytogenes use multidrug efflux pumps to export small molecules into the host cytoplasm; strains with higher expression of these pumps have more induction of interferon-β. Although the host sensor is unknown, the activation pathway does not require the adaptors MyD88, TRIF or MAVS. Identification of this intracellular bacterial ‘alarmin’ should facilitate the search for the cytosolic sensor. LAD Science express (27 May 2010) doi:10.1126/science.1189801

New MHCII receptor

A family of receptors related to immunoglobulin Fc receptor molecules is expressed on cytotoxic lymphocytes but fails to bind immunoglobulin molecules. No ligands are known for these Fc receptor-like receptors (FCRLs). In the Journal of Immunology, Davis and colleagues identify the major histocompatibility complex (MHC) antigen HLA-DR as the ligand for human FCRL6. Both HLA-DRα and HLA-DRβ chains are required for recognition. FCRL6 shows differences in binding to HLA-DRβ chains, with HLA-DRβ3 binding less well than HLA-DRβ1 or HLA-DRβ4. Although FCRL6 contains a cytosolic immunoreceptor tyrosine-based inhibitory motif that can recruit phosphatases after its phosphorylation, no inhibitory function has yet been associated for this receptor. Further mechanistic studies are needed to elucidate the function(s) of FCRL–MHC class II interactions. LAD J. Immunol. (2 June 2010) doi:10.4049/jimmunol.1000832

Building a nest

RNA viruses are known to remodel intracellular membranes to generate specialized sites for replication. In Cell, Hsu et al. show that plus-stranded RNA viruses can manipulate components of the cellular secretory pathway to generate organelles that are distinct from the host cell in their protein and lipid composition. Specific viral proteins, such as enteroviral protein 3A, modulate the small Ras-family GTPase Arf1 and its guanine nucleotide-exchange factor GBF1 to promote ‘preferential’ recruitment of phosphatidylinositol-4,5-bisphosphate to membranes. This recruitment yields organelles enriched in phosphatidylinositol-(4,5)-phosphate lipid, which facilitate viral RNA synthesis. Inhibition of phosphatidylinositol-4,5-bisphosphate kinase IIIβ interferes with this process. Two distinct types of plus-stranded RNA viruses can remodel the secretory pathway to generate organelles with unique protein and lipid composition geared for viral RNA replication. IV Cell 141, 799–811 (2010)

Potent HIV antibody structure

The elicitation of broadly cross-reactive antibodies able to neutralize most isolates of human immunodeficiency virus (HIV) remains an important challenge for vaccination. Now in the Proceedings of the National Academy of Science Wilson and colleagues have clarified the Fab crystal structure of one such antibody: PG16. This antibody, cloned from an HIV-infected donor, has a potent, broad neutralizing ability. Its binding region has an unusual structure characterized by an exceptionally long complementarity-determining region 3 that forms a stable loop subdomain reaching out over the antibody surface. Because of its appearance, this unique structure is called the ‘hammerhead’, and a seven–amino acid sequence contained in it is conserved by the Fab crystal structure of one such antibody: PG16. This antibody, cloned from an HIV-infected donor, has a potent, broad neutralizing ability. Its binding region has an unusual structure characterized by an exceptionally long complementarity-determining region 3 that forms a stable loop subdomain reaching out over the antibody surface. Because of its appearance, this unique structure is called the ‘hammerhead’, and a seven–amino acid sequence contained in it is conserved by the antibody's fine specificity of antigen recognition. It remains to be determined whether this structure is a prerequisite for other broadly neutralizing antibodies. These findings could have important implications for the design of therapeutic monoclonal antibodies. ZF Proc. Natl. Acad. Sci. USA (7 May 2010) doi:10.1073/pnas.1004600107

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