Autoimmunity thresholds

Low-avidity autoreactive T cells exist in the periphery as part of a normally selected repertoire. In the *Journal of Experimental Medicine*, Enouz *et al.* generate a transgenic mouse that expresses a TCR that is at the threshold between thymic negative and positive selection by a tissue-restricted antigen to study the activation threshold and functional characteristics of low-avidity autoreactive T cells. The authors report that such T cells are not anergic, respond to peripheral self antigen during systemic viral infection, form functional memory T cells and can expand their numbers and induce autoimmunity. Moreover, these cells are activated in the periphery by much less potent ligands, which suggests a difference between the threshold for negative selection in the thymus and that for peripheral T cell activation. The cause of this gap between the safety margin 'imprinted' by the thymus and the threshold for peripheral activation remains unknown. ***IV***

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NET benefits

Neutrophil extracellular traps (NETs) are tangles of DNA impregnated with proteolytic molecules and are released ('NETosis') by neutrophils as these cells die in response to bacterial or fungal infection. In *Nature Medicine*, Kubes and colleagues investigate 'NETosis' *in vivo* and its contribution to the control of infection. Intravital microscopy of skin shows rapid (<2 hours) NETosis specifically in response to bacterial challenge but not in response to sterile inflammation. NETosis occurs only in tissue parenchyma but not in the vasculature, presumably to limit widespread and potentially pathogenic dissemination of NETs. Furthermore, signaling via Toll-like receptor 2 and complement receptors is required for NETosis, although specific stimulation of either of these pathways is not sufficient to trigger NETosis. Interestingly, neutrophils undergoing NETosis continue chemotaxis and phagocytosis, a previously unappreciated degree of multitasking for 'NETosing' cells. Finally, inhibiting NET formation *in vivo* exacerbates bacteremia, which demonstrates the importance of this process to microbial control. *ZF*

Nat. Med. **18**, 1386–1393 (2012)

Allies for weight loss

Invariant natural killer T cells (*i*NKT cells) have immunoregulatory roles in physiological and pathological settings. In *Immunity*, Lynch *et al.* show that *i*NKT cells regulate body weight and metabolic state by modulating inflammation in adipose tissue. Healthy human and mouse adipose tissues show considerable enrichment for *i*NKT cells but these cells are replaced by inflammatory macrophages as the adipose tissue expands during obesity. Mice that lack *i*NKT cells, such as $J_{\alpha}18$- or CD1d-deficient mice, have enhanced weight gain, insulin resistance and fatty livers when kept on a high-fat diet, relative to that of their wild-type counterparts. Adoptive transfer of *i*NKT cells or activation of *i*NKT cells through injection of α-galactosylceramide decreases body fat and improves insulin sensitivity in mice fed a high-fat diet. The *i*NKT cells may directly affect adipocytes or act indirectly by modulating macrophage function through their production of anti-inflammatory cytokines such as interleukin 4 (IL-4) and IL-10. ***IV***

***Immunity* 37, 574–587 (2012)**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Intrinsic neuronal immunity

Neurons are the target of many important viruses, yet their intrinsic mechanisms of resistance are relatively poorly understood. In *Cell Host and Microbe*, Iwasaki and colleagues find that neurons engage in autophagocytosis to control infection with herpes simplex virus type 1 (HSV-1). Neurons produce little if any type I interferon (IFN-α/β) after HSV-1 infection; furthermore, neurons are less responsive to IFN-α/β-induced cell death than are mitotic cells such as fibroblasts. Accordingly, neurons exposed to IFN-α/β also fail to induce the interferon-stimulated gene *Mx1*. Instead, neuronal resistance to HSV-1 seems to rely on active autophagy. Using a genital-tract model of HSV-1 infection, the authors observe that disease outcome is independent of autophagocytosis in the epithelial compartment. Mutant virus unable to regulate autophagocytosis shows impaired replication in neurons and less dissemination of infection. More directly, neurons isolated from mice deficient in autophagocytosis show greater infection *in vitro*. *ZF*

Cell Host Microbe **3**, 334–345 (2012)

Strategic locations

Lymph delivers antigen-bearing dendritic cells (DCs), viral particles and extracellular bacteria to draining lymph nodes where T cells and B cells are primed. In *Cell*, Kastenmüller *et al.* and Sung *et al.* show how rapid cellular communication in lymph nodes helps to contain infectious agents. Infection of subcapsular macrophages at afferent lymph portals activates caspase-1 and the release of IL-18 and IFN-α/β. Within hours, NK cells, NKT cells and γδ T cells adjacent to those infected macrophages respond by producing IFN-γ, which in turn acts to recruit neutrophils and inflammatory monocytes into the infected lymph node. This response limits viral spread before the activation of naive antigen-specific lymphocytes. Similarly, during recall challenge, $CXCR3^+$ central memory T cells are rapidly mobilized in lymph nodes by responding to subcapsular macrophage production of the chemokines CXCL10 and CXCL9. This faster mobilization to the site of viral infection, here in the lymph node, explains in part the greater efficiency of memory T cell responses than of primary T cell responses. ***LAD***

***Cell* 150, 1235–1248 & 1249–1263 (2012)**

Composite AICE recognition

The related transcription factors IRF4 and IRF8 regulate key processes in DCs, B cells and T cells, yet both have weak DNA-binding activity and thus must interact with other factors. In *Nature* and *Science*, Murphy, Leonard and Singh show that BATF proteins, a family of AP-1-like transcription factors, recruit IRF4 and IRF8 to DNA-binding sites (AICE motifs) in T cells and DCs. Motif-discovery analyses identify two composite elements that differ only by spacing between the half-sites. Both BATF and IRF4 are needed to drive high expression of *Il17*, *Il10* and *Ctla4* in T cells. BATF expression, induced by IFN-γ during infection, can rescue the development of $CD8\alpha^+$ and $CD103^+$ DCs in BATF3-deficient mice. The leucine-zipper domain of BATF proteins is necessary for interaction with IRF4, as substitution of His55 impairs the BATF-IRF4 interaction. These findings show how distinct gene-expression programs can be turned on through the recognition of composite sites. *LAD*

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