Sequestering CD3ε ITAMs

Many cell surface receptors signal through cytoplasmic immunoreceptor tyrosine-based activation motifs (ITAMs). In *Cell*, Wucherpfennig and colleagues evaluate the functional relevance of membrane binding by ITAMs, a phenomenon described before, by using the CD3ε cytoplasmic domain (CD3εCD) of the T cell antigen receptor (TCR) as an example. Fluorescence resonance energy transfer shows close interaction of CD3εCD with the plasma membrane in T cells and that both basic and hydrophobic residues of CD3εCD contribute to this interaction. Multidimensional nuclear magnetic resonance spectroscopy of the lipid-bound state of CD3εCD shows that four hydrophobic residues of the CD3εCD ITAM are inserted into the hydrophobic interior of the plasma membrane lipid bilayer, which prevents accessibility of non-ligand-bound TCR-CD3εCD ITAM tyrosine residues to phosphorylation by kinases associated with TCR activation. Whether sequestration of the key ITAM residues into the hydrophobic core of a lipid bilayer regulates other ITAM-bearing receptors is unclear. ***DCB***

***Cell* 135, 702–713 (2008)**

De-adhering leukocytes

Leukocytes enter inflamed tissues by means of integrin activation and adhesion to the endothelium. In *Science*, Chavakis and colleagues identify the glycoprotein Del-1 as an endogenous inhibitor of the integrin LFA-1. Soluble Del-1 blocks neutrophil adhesion in flow conditions *in vitro* and results in the recruitment of many fewer neutrophils to the peritoneum after thioglycollate challenge. Del-1-deficient mice, in contrast, have more neutrophils in lung infiltrates after instillation of lipopolysaccharide or tumor necrosis factor. The greater neutrophil recruitment is reversed in mice doubly deficient in Del-1 and LFA-1. Expression of Del-1 seems to be regulated, as inflammatory signals transiently decrease its expression in endothelial cells. Details of this regulation as well as the mechanism of inhibition of LFA-1 function remain to be determined. *LAD*

Science 322, 1101–1104 (2008)

Aire dampens B cells

The transcriptional regulator Aire mediates central tolerance mechanisms in the T cell lineage. In the *Proceedings of the National Academy of Science*, Lindh *et al.* show that Aire also serves a prominent function in regulating T cell–independent B cell responses. *Aire*$^{-/-}$ mice have higher titers of autoantibodies and symptoms of B cell–mediated autoimmunity. This phenotype is linked to higher expression of B cell–activating factor, which is expressed more abundantly in Aire-deficient monocyte-derived dendritic cells than in wild-type cells. The higher expression is triggered by IFN-γ and transcription factor STAT1 pathways, which are negatively regulated by Aire. Human patients with autoimmune polyendocrine syndrome type I have similar enhanced T cell–independent autoimmunity linked to higher expression of B cell–activating factor. How Aire regulates the STAT1 signaling pathway in B cells remains unknown at this time. ***LAD***

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Counteracting T_{reg} cell conversion

The mechanism by which retinoic acid amplifies transforming growth factor-β (TGF-β)-induced expression of the transcription factor Foxp3 in naive CD4$^+$ T cells is not understood. In *Immunity*, a team led by Mathis and Benoist report that retinoic acid boosts Foxp3 expression—and thus conversion of regulatory T cells—indirectly. By signaling through its receptor RARα, retinoic acid enhances TGF-β-induced expression of Foxp3 in splenic CD4$^+$ T cells *in vitro*. However, the presence of CD44^{hi}CD4$^+$ T cells blunts TGF-β-induced expression of Foxp3 in naive CD4$^+$ T cells. Retinoic acid, by suppressing CD44^{hi}CD4$^+$ T cell production of cytokines, including interleukin 4, that counteract the effects of TGF-β, overrides CD44^{hi}CD4$^+$ T cell–mediated inhibition of Foxp3 expression in naive CD4$^+$ T cells. Confirming the indirect nature of this process, retinoic acid–mediated amplification of TGF-β-induced Foxp3 expression requires RARα expression in CD44^{hi} but not naive CD4$^+$ T cells *in vitro* and *in vivo*. *CB*

Immunity **29**, 758–770 (2008)

T cell vaccine for SIV

Vaccines for human and simian immunodeficiency virus (SIV) based on adenovirus serotype 5 (rAd5) vectors have thus far failed to induce protective immune responses. In *Nature*, Barouch and colleagues evaluate the effectiveness of a heterologous prime-boost strategy against SIV infection by using vectors of serotype rAd26 or rAd5 that express the SIV Gag protein. Priming of monkeys with rAd26-Gag and boosting with rAd5-Gag elicits greater polyfunctional CD8$^+$ and CD4$^+$ T cell responses than does the rAd5-rAd5 prime-boost regime. Challenge with SIV 6 months after the boost immunization shows that monkeys vaccinated with rAd26-rAd5 have sustained partial control of set-point viral loads, slower decreases in CD4$^+$ T cell numbers, preservation of central memory CD4$^+$ T cells and more rapid kinetics of Gag-specific antibody responses. By durably improving the magnitude, breadth and functionality of cellular immune responses to SIV challenge, the heterologous rAd26-rAd5 prime-boost strategy may yield important new insights for the generation of vaccines for other retrovirus infections. ***DCB***

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Antiparasitic Atg5

Eradication of parasites from mammalian hosts is mediated by autophagy, a process known to require interferon-γ (IFN-γ). In *Cell Host & Microbe*, Virgin and colleagues assess the function of the autophagy protein Atg5 in parasite elimination *in vivo*. Mice that lack Atg5 in macrophages and granulocytes succumb more rapidly than wild-type mice to infection with *Toxoplasma gondii* and *Listeria monocytogenes*. Treatment with IFN-γ and lipopolysaccharide results in fewer *T. gondii* parasites per parasitophorous vacuole in wild-type and Atg5-deficient macrophages. However, wild-type but not Atg5-deficient macrophages treated with IFN-γ and lipopolysaccharide show disruption of the parasitophorous vacuole membrane and elimination of the remaining parasites. This membrane destruction does not seem to involve autophagosome formation but is associated with recruitment of the IFN-γ-inducible GTPase IIGP1 and lysosome-like vesicles. Additional work is needed to determine how Atg5, by a mechanism apparently independent of its function in autophagy, recruits IIGP1 to parasitophorous vacuoles. *CB*

Cell Host Microbe **4**, 458–469 (2008)