TRIMing infections with antibodies

Antibodies are typically thought to act in the extracellular space by specifically binding pathogens and triggering effector functions. In the *Proceedings of the National Academy of Sciences*, James and colleagues delineate a mechanism by which antibodies can still mediate pathogen neutralization even in the cytosol of a cell. In an adenovirus infection model *in vitro*, they observe that virus bound by antibody extracellularly still remains bound in the cytosol after infection of the cell. In the cytoplasm, the antibody invariant region then rapidly recruits the cytosolic immunoglobulin receptor TRIM21. Not only does TRIM21 bind with an affinity higher than that of any other immunoglobulin receptor, its E3 ubiquitin ligase activity targets the virus-antibody complex for degradation via the proteasome. TRIM21 binds to IgG and, with a lower affinity, to IgM, which suggests that this mechanism is applicable to various isotypes and multiple infection stages. Intracellular degradation via TRIM21 thus represents the last line of defense in antibody-mediated pathogen neutralization. ***ZF***

Proc. Natl. Acad. Sci. USA **107, 19985–19990 (2010)**

TRAF3 suppresses IL-17R

IL-17 activates both NF-κB and mitogen-activated protein kinase pathways via IL-17 receptors to elicit the expression of inflammatory cytokines and chemokines. In the *Journal of Experimental Medicine*, Zhu *et al.* show that the adaptor molecule TRAF3 transiently associates with the receptors IL-17RA and IL-17RC to suppress IL-17-induced gene expression. TRAF3 binds to the distal domain of the IL-17 receptors after IL-17 ligation. TRAF3 interaction blocks the binding of IL-17R to Act1 and TRAF6, which act together to promote activation of NF-κB and the kinase Jnk; however, Act1 and TRAF3 bind to different cytoplasmic domains of IL-17R, which suggests that inhibition might occur by allosteric modulation. Increasing the abundance of TRAF3 decreases both IL-17 signaling and sensitivity of mice to IL-17-dependent inflammatory disease. How IL-17 ligation exposes the TRAF3-interaction site on IL-17R and whether TRAF3 can dissociate assembled IL-17R–Act1–TRAF6 complexes to limit IL-17 signaling remain to be determined. *LAD*

J. Exp. Med. **207**, 2647–2662 (2010)

Notch goes ligand independent

How loss of the transcription factor Ikaros leads to activation of the Notch receptor in T cell acute lymphoblastic leukemia is unknown. In *Immunity*, Gómez-del Arco *et al.* identify alternative 5′ and intergenic Notch1 promoters that drive the expression of Notch 1 isoforms with accelerated or constitutive cleavage. Ikaros represses these noncanonical promoters at the epigenetic level, which explains the aberrant activation of Notch signaling in Ikaros-deficient leukemias. These alternative promoters produce proteins that lack the signal peptide or the entire ligand-binding domains and are constitutively cleaved by ADAM metalloproteinases and γ-secretases. Both the 5′ alternative and canonical promoters are active during the double-negative 3 stage of T cell development, which correlates with high Notch activity. The noncanonical promoters are repressed at the double-positive stage, which suggests developmental regulation of this alternative, ligand-independent Notch activation. ***IV***

Immunity **33, 685–698 (2010)**

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

Immunity shapes parasites

Parasites elicit robust immune responses in their hosts, yet there is provocative evidence suggesting that this can sometimes enhance rather than impair parasite development. To address this apparent paradox, Allen and colleagues in *PLoS Biology* investigate how host immunity affects the development of a filarial nematode. Anti-filarial responses are typified by eosinophilia and IL-5. Those nematodes that do survive inoculation into normal hosts show accelerated development compared with that of nematodes in hosts deficient in either eosinophils or IL-5. The intact immune response of normal hosts does not seem to select fitter nematodes but instead elicits an eosinophil-dependent developmental reaction by the parasite. This kind of plasticity in response to environmental cues, in this case eosinophilia, is consistent with the life-history theory, which suggests that natural selection shapes an organism to maximize the number of offspring. These findings have important implications for vaccines since, in the absence of sterilizing immunity, vaccines might increase the amount of parasite transmission. *ZF*

PLoS Biol. **8**, e1000525 (2010)

Distinguishing self

The cellular mRNA of higher eukaryotes and many viral RNAs are methylated at the N-7 and 2′-O positions on the 5′ guanosine cap. Whereas N-7 methylation is essential for the translation and stability of RNA, the function of 2′-O methylation remains unclear. In *Nature*, Diamond and colleagues show that 2′-O methylation of viral RNA restricts the antiviral effects of IFIT proteins, which are interferon-stimulated molecules linked to the inhibition of viral replication. West Nile virus mutants that lack 2′-O methyltransferase activity are attenuated in wild-type primary cells and mice but are pathogenic in the absence of type I interferon signaling. The mutation does not affect pathogen sensing through the RIG-I sensor or interferon induction. Similar effects are observed with vaccinia and mouse herpes virus, which suggests that 2′-O methylation of viral RNA may have evolved to allow viruses to evade cellular mechanisms that distinguish self from non-self. ***IV***

Nature **468, 452–456 (2010)**

Germinal center dynamics

Germinal centers arise after immunization or infection and facilitate T cell–B cell interactions necessary for the promotion of immunoglobulin affinity maturation. The selection and proliferation of B cells occur in germinal centers, but knowledge of how these processes are regulated remains rudimentary. In *Cell*, Nussenzweig and colleagues report the development of a photoactivatable green fluorescent protein reporter that allows the identification and isolation of distinct activated B cell populations for elucidation of the interactions that regulate selection and can functionally distinguish B cell activity in the light and dark zones of germinal centers. B cell proliferation occurs mainly in the dark zone, whereas T cell–B cell interactions occur in the light zone. Although dark-zone B cells can readily migrate to the light zone, fewer light-zone B cells migrate to dark zones, which suggests that this interzonal migration is due to selection. B cells of higher affinity or those presenting more cognate peptide to T cells are selected to migrate and accumulate in the dark zone. These results suggest that selection occurs because of competition for T cell interaction. Which trafficking molecules underlie this selective migration deserves further study. *LAD*

Cell **143**, 592–605 (2010)