Nonmonogamous antibodies

Antibodies can typically crosslink epitope-bearing antigens, owing to their dimeric Fab structure constructed of two identical immunoglobulin heavy and light chains. In *Science*, Parren and colleagues show that human immunoglobulin G4 (IgG4) antibodies readily exchange heavy- and light-chain subunits *in vivo*. This ability resides in the C_H3 domain of the IgG4 heavy chain. The resulting antibodies retain the classic 'Y structure', but the Fab arms differ from each other, each derived from the parental IgG4. Thus, antigenic specificity is retained by each Fab, but the ability to crosslink identical epitopes is lost, which can limit antibody efficacy. The authors discuss their results in terms of why IgG4 antibodies might naturally arise to dampen potentially damaging antibody responses and the implications on various IgG4 therapeutic approaches now underway. ***LAD***

***Science* 317, 1554–1557 (2007)**

Sensing self

In healthy animals, plasmacytoid dendritic cells (pDCs) release type 1 interferon after Toll-like receptor 9–mediated recognition of viral and microbial but not self DNA. In *Nature*, Gilliet and colleagues show that LL37, an endogenous cationic antimicrobial peptide with higher expression in psoriatic than in healthy skin, converts self DNA into an agent capable of eliciting interferon from pDCs. Neutralization of LL37 or digestion of DNA in psoriatic skin lesions suppresses pDC production of interferon. LL37 binds to, aggregates and transports DNA into early endosomes of pDCs, probably through ionic interactions. Toll-like receptor 9 molecules present in these membrane-bound compartments detect LL37–self DNA complexes and trigger production of type I interferon. How LL37 directs self DNA specifically to early endosomes, and whether LL37 initiates the release of type I interferon and exacerbates autoimmune disorders in other tissues, is not yet known. *CB*

Nature (16 September 2007) doi:10.1038/nature 06116

Adaptive tempers innate

Immune responses occur in a temporal order, with early innate responses being required to induce effective later adaptive responses. In *Nature Medicine*, Fu and colleagues show that adaptive immune cells can also be critical for control of the innate immune response. Evaluating the explanation for the death of nude mice after sublethal infection with an RNA virus, the team stimulated wild-type and nude mice with the Toll-like receptor 3 ligand poly(I:C) to show that the latter mice rapidly die from 'cytokine storm'—the expression of lethal amounts of cytokines such as tumor necrosis factor. By depletion of various immune cell subsets and specific cytokines, they show that innate immune cell production of tumor necrosis factor leads to the rapid death of T cell–depleted or nude mice. The addition of nonregulatory T cells suppresses the production of lethal tumor necrosis factor, and this effect requires cell-cell contact. Thus, T cells are necessary and sufficient for 'tempering' innate cell production of lethal, cytokine storm–producing inflammation. ***DCB***

***Nat. Med.* (23 September 2007) doi:10.1038/nm163**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Blunting IL-1β release

The transcription factor NF-κB is central to mediating inflammatory responses, so inhibiting NF-κB activation might be beneficial for stemming inflammatory diseases. In *Cell*, Karin and colleagues disprove this hypothesis. Mice treated with lipopolysaccharide (LPS) die faster when NF-κB activation is blocked. Such toxicity is due to copious release of interleukin 1β (IL-1β) from neutrophils and myeloid cells. NF-κB activation increases the expression of inhibitors of caspase 1, which is used in macrophage 'inflammasomes' to cleave pro-IL-1β to its active form. NF-κB likewise upregulates serpin expression in neutrophils to block serine protease activity, which these cells use mainly to activate IL-1β. Such responses might have evolved to counteract attempts of viruses and bacteria to evade the immune system. These findings suggest targeting NF-κB might lead to severe unintended consequences. *LAD*

Cell **130**, 918–931 (2007)

Silencing the silencer

The transcription factors Runx1 and Runx3 directly activate the *Cd4* silencer in developing thymocytes. In the *Journal of Immunology*, Bosselut and colleagues investigate the mechanism by which Zbtb7b (also called Th-POK), a transcription factor essential for commitment to the $CD4^+$ T cell lineage, antagonizes Runx-mediated *Cd4* silencing. Although incapable of promoting *Cd4* expression on its own, Zbtb7b blocks Runx3- and Runx1-induced *Cd4* silencing in transfected cell lines and in thymocytes. As Zbtb7b-induced reversal of Runx3-mediated *Cd4* suppression is abolished in the presence of a histone deacetylase inhibitor, Zbtb7b may act indirectly, by repressing the expression of factors essential for Runx-mediated *Cd4* repression. These observations render unlikely a scenario in which Runx3 and Zbtb7b directly compete for binding to the *Cd4* silencer and explain how *Cd4* expression is maintained in Runx1-expressing mature $CD4^+$ T cells. Identification of Runx corepressors whose expression might be suppressed by Zbtb7b remains for future study. ***CB***

***J. Immunol.* 179, 4405–4414 (2007)**

Aire terminates proliferation

Thymic medullary epithelial cells (MECs) are critical for central tolerance through their expression of autoimmune regulator (Aire), a transcription factor required for expression of peripheral tissue antigens (PTAs) during the development of αβ T cells. In the *Journal of Experimental Medicine*, Mathias and colleagues test whether $Aire^+$ MECs represent 'end-stage' cells that express diverse PTAs, having differentiated to that state over time, or instead represent early precursors that cycle to produce $Aire^-$ progeny with more restricted PTA expression. To determine which model is accurate, they use pulse-chase incorporation of bromodeoxyuridine (BrdU) coupled with staining with monoclonal antibody to Aire to evaluate the percentage of cycling $Aire^+$ MECs at various times. They find that $Aire^+$ MECs do not cycle and that $Aire^-BrdU^+$ cells give rise to $Aire^+BrdU^+$ cells. In addition, $Aire^+$ MECs rapidly 'turn over', and overexpression of Aire in a MEC line increases apoptosis. These data suggest that Aire expression occurs relatively late in MEC development and fosters the rapid turnover of MECs by apoptosis. *DCB*

J. Exp. Med. (1 October 2007) doi:10.1084/jem.20070795