Ploidy spotting

An indiscriminate increase in cellular DNA content (hyperploidy) is an important contributor to oncogenesis because of its genome-destabilizing effects. In *Science*, Kroemer *et al.* identify a mechanism whereby the immune system recognizes and controls hyperploid cells. Cytotoxic agents can elicit immunogenic tumor killing, but this requires an endoplasmic reticulum stress response that translocates calreticulin to the plasma membrane. The authors find that hyperploidy also correlates closely with the translocation of calreticulin. Hyperploid tumors grafted to immunocompetent mice are destroyed by the immune system, but this depends on the surface expression of calreticulin. Finally, patients with breast cancer that responds to cytotoxic drugs have a lower DNA content than do unresponsive patients, which suggests that the tumors are immunoselected by the rejection of calreticulin-positive hyperploid cells. The immune system can therefore detect an important cellular property associated with cancerous transformation through the expression of calreticulin on target cells. ***ZF***

***Science* 337, 1678–1684 (2012)**

Default fate

Low constitutive expression of the transcription factor GATA-3 in naive T cells and the fact that dendritic cells do not produce interleukin 4 (IL-4) are consistent with the idea of a default T helper type 2 (T_H2) program for $CD4^+$ T cells. In *Immunity*, Zhou *et al.* show that many redundant pathways induce expression of the T_H1 transcription factor T-bet, but in the absence of T-bet, activated T cells default into an endogenous T_H2 program characterized by GATA-3 upregulation and IL-4 production by T cells. IL-12 and interferon-γ are redundant for the induction of T-bet expression in cells responding to signaling via the T cell antigen receptor (TCR). In the absence of T-bet, which inhibits the expression of GATA-3 and IL-4, GATA-3 drives T_H2 differentiation even in the absence of IL-4. Stimuli other than IL-12 and interferon-γ can also induce T-bet *in vivo*; type I interferon or IL-27 represent possible candidates. *IV*

Immunity **37**, 660–673 (2012)

Vaccine strategies

Tissue-resident memory T cells provide better protection at peripheral sites than do circulating memory T cells, but their entry into tissues is controlled by inflammation or infection. In *Nature*, Shin and Iwasaki apply a 'prime-and-pull' vaccine strategy to enhance the recruitment of circulating activated T cells, generated by subcutaneous vaccination, into the genital-tract mucosa. In a model of subcutaneous immunization of mice with herpes simplex virus type 2 (HSV-2), topical application of the chemokines CXCL9 and CXCL10 induces the recruitment of HSV-specific effector $CD8^+$ and $CD4^+$ T cells to the genital tract. A stable $CD8^+$ memory T cell population is maintained locally after chemokine 'pull' and protects mice against spreading of the virus to the sensory neurons and the development of clinical symptoms during genital infection with HSV-2. This strategy could be a promising approach for protection against sexual transmitted diseases, including infection with human immunodeficiency virus. ***IV***

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

Regulating LUBAC

Linear polyubiquitination is mediated by the LUBAC protein complex and can direct signaling by the transcription factor NF-κB; however, the regulation of LUBAC-mediated linear ubiquitination is unclear. Two papers in *EMBO Journal,* by Beyaert *et al.* and Nureki *et al.*, demonstrate how the deubiquitinating factor A20 can control LUBAC function and NF-κB activity. Both groups find that A20 rapidly associates with LUBAC polyubiquitination chains after triggering of the receptor for tumor-necrosis factor and arrest NF-κB signaling. This inhibition seems to operate through the ability of A20 to compete with binding of the NF-κB pathway adaptor NEMO to LUBAC. The seventh zinc-finger domain of A20 (ZF7) is crucial for the association with LUBAC, and ZF7 polypeptides alone are sufficient to regulate NF-κB. Nureki *et al.* crystallize the ZF7–linear polyubiquitin complex and observe that binding occurs via a structure formed by two connected ubiquitin units. This mechanism of NF-κB regulation therefore seems to operate independently of its deubiquitination activity. *ZF*

EMBO J. **31**, 3845–3855 and 3856–3870 (2012)

Macrophage regulation

Hypercholesterolemia, a risk factor linked to chronic inflammation and atherosclerosis, is associated with an accumulation of macrophage foam cells in arterial lesions. In *Cell*, Spann *et al.* report the surprising finding that excess free cholesterol suppresses the expression of genes encoding proinflammatory molecules in mouse and human macrophages. Quantitative transcriptional and lipidomic analyses shows that cholesterol metabolism is regulated by desmosterol, an agonist of LXR (a member of the nuclear receptor family of transcription factors). Desmosterol concentrations increase during hypercholesterolemia. High concentrations of desmosterol inhibit the expression of *Il1b*, *Nos2*, *Cxcl9* and *Cxcl10* by activating LXR-mediated mechanisms that suppress the histone acetylation necessary for gene expression. These findings challenge the conventional assumption that foam cells are the source of inflammatory mediators in atherosclerosis and prompt further investigation to determine how inflammation arises. ***LAD***

***Cell* 151, 138–152 (2012)**

Aging T cells

Elderly humans mount weaker immune responses after infection or vaccination than do younger humans. In *Nature Medicine*, Goronzy and colleagues identify age-related defects in TCR signaling capacity that lessens the ability to recruit naive $CD4^+$ T cells into immune responses. The lower TCR sensitivity in T cells from elderly people (>70 years of age) is due to higher expression of the dual-specific phosphatase DUSP6, which regulates activation of the kinase Erk and leads to less phosphorylation of Erk after TCR stimulation. This scenario increases the antigenic threshold needed to activate naive T cells. DUSP6 expression is regulated by the microRNA miR-181a. T cells from older humans have lower miR-181a expression than do those from young adults. The responsiveness of naive T cells can be restored by lowering DUSP6 expression or inhibiting its activity with the pharmacological inhibitor BCI. These findings suggest a means of boosting adaptive immunity in the elderly by targeting DUSP6. *LAD*

Nat. Med. **18**, 1518–1524 (2012)