Planting seeds of defense

Pathogen infection of plants can trigger programmed cell death (PCD) of infected tissues in a process called the hypersensitive response. Plants require caspase-like activities to initiate PCD, but the genes encoding these proteins have not been identified. In *Science*, Hatsugai *et al.* show that vacuolar processing enzyme (VPE) from tobacco has a caspase 1–like activity. VPE deficiency in tobacco plants prevented PCD induced by tobacco mosaic virus infection. Similarly, Rojo *et al.* in *Current Biology* show VPEγ expression in *Arabidopsis* was induced after infection with *Pseudomonas syringae*, *Botrytis cinera* or turnip mosaic virus, whereas VPEγ deficiency increased host susceptibility to these pathogens. These studies show VPEs are the 'caspase equivalents' for plant cell death. *JDKW*

***Science* 305, 855–858 (2004), *Curr. Biol.* (23 September 2004) doi: 10.1016/S0960982204007523**

Venom of the Spanish flu

Why the 1918 'Spanish' influenza virus had unprecedented virulence is unclear. In *Nature*, Kobasa *et al.* test the pathogenicity of hemagglutinin (H^{sp}) and neuraminidase (N^{sp}) from the 1918 virus by producing a panel of recombinant viruses containing genes encoding these molecules. H^{sp}, but not N^{sp}, conferred enhanced virulence to the three strains of influenza virus examined. H^{sp} enhanced the ability of the viruses to disseminate throughout mouse lungs without increasing viral replication. In addition, H^{sp} viruses activated macrophages to produce proinflammatory cytokines and chemokines. These observations provide a platform to better understand the mechanisms behind lethal infectivity of the virus and thus achieve rational design of appropriate control measures. *PTL*

Nature **431**, 703–707 (2004)

Dampening TLR9 signals

Activation of the kinase Erk is dependent on the serine-threonine kinase Cot during lipopolysaccharide-induced Toll-like receptor 4 (TLR4) signaling in macrophages. In the *Journal of Clinical Investigation*, Sugimoto *et al.* investigate the involvement of Cot in other TLR-mediated pathways. The TLR9 ligand dinucleotide CG (CpG DNA) unexpectedly induced Cot-independent Erk activation and stimulated more interleukin 12 (IL-12) production by Cot-deficient macrophages or dendritic cells than by wild-type cells. Induction of c-Maf and GAP-12, two known repressors of IL-12 p40 mRNA expression, were inhibited in Cot-deficient macrophages. *In vivo*, Cot-deficient mice showed enhanced T helper type 1 (T_H1) responses to immunization with ovalbumin and leishmania challenge. Thus, Cot seems to act as a negative regulator of IL-12-mediated T_H1 responses. The exact mechanism of how Cot functions as a negative regulator remains to be elucidated. *JDKW*

J. Clin. Invest. **114**, 857–866 (2004)

MTA3 blocks plasma cells

The transcriptional repressor Bcl-6 maintains mature B lineage gene expression and prevents plasma cell differentiation induced by the antagonizing gene repressor Blimp-1. In *Cell*, Fugita *et al.* find MTA3, a component of the NuRD nucleosome remodeling complex, associates with Bcl-6 in B cells. Bcl-6 has two separate repressor domains: one previously identified as an N-terminal BTB-POZ region, and a central domain that interacts with MTA3. Acetylation of key Bcl-6 lysine residues in the latter domain blocks MTA3 interaction. MTA3 overexpression reverses the plasma cell phenotype; conversely, blocking MTA3 expression in B cells derepresses expression of plasma cell markers. Together, MTA3 and Bcl-6 regulate terminal differentiation of B cells. *LAD*

Cell **119**, 75–86 (2004)

CHIP shots for E2A destruction

Lymphocyte fate selection is determined by the relative amounts of E2A and Notch proteins. Notch signaling induces Erk MAP kinase phosphorylation of E2A proteins, targeting them for ubiquitination and proteasome-mediated destruction. In *Molecular and Cellular Biology*, Sun and colleagues identify CHIP as an essential component required for E2A ubiquitination. CHIP binds E2A, but this recognition does not require E2A phosphorylation. CHIP recruits the chaperones Hsc70 and Skp2, components of the ubiquitin E3 ligase complex SCF^{Skp2}, to E2A in a pre-ubiquitination complex. Notch-induced E2A phosphorylation strengthens this protein interaction and facilitates the assembly of a ubiquitination-competent SCF^{skp2} complex. Thus, CHIP is poised to regulate E2A stability in response to Notch receptor ligation. *LAD*

Mol. Cell. Biol. **24**, 8951–8962 (2004)

Maintaining HSC function

Hematopoietic stem cells (HSCs) express Gfi-1, a zinc finger transcription factor known to promote T cell proliferation. In *Nature* Orkin and colleagues and in the *EMBO Journal* Moroy and colleagues investigate the function of Gfi-1 in HSCs. Unexpectedly, Gfi-1-deficient mice had hyperproliferative HSCs. Gfi-1 deficiency decreased long-term and competitive reconstitution of HSCs. Orkin and colleagues found, using chimeric mice generated from $Gfi1^{-/-}$ and $Gfi1^{+/-}$ embryonic stem cells, that $Gfi1^{+/-}$ bone marrow cells 'out-compete' $Gfi1^{-/-}$ cells. Moroy and colleagues also show the defects of Gfi-1-deficient HSCs are cell autonomous rather than being a secondary effect of an impaired hematopoietic microenvironment. Thus Gfi-1 is pivotal for restricting HSC proliferation and maintaining HSCs' capacity for self-renewal and multilineage differentiation. *JDKW*

EMBO J. (23 September 2004) doi: 10.1038/sj.emboj.7600419, *Nature* (30 September 2004) doi: 10.1038/nature02994

Cytokine receptor regulation

The Mgat family of Golgi enzymes trim and remodel N-glycans that are associated with glycoproteins. Deficiency in Mgat results in reduced viability and tissue defects in mice. In *Science*, Partidge *et al.* observed that cells with active membrane remodeling, such as tumor cells, are less responsive to cytokines in the absence of Mgat5. Mgat5 promotes the association of cytokine receptors with galectin-3 to form a lattice on the cell surface and hence delays receptor endocytosis. By regulating the cytokine receptors, Mgat5 enhances cell motility required for tumor cell metastasis. In addition, Mgat5 is important in macrophage activation through cytokine receptor signaling, phagocytosis and migration *in vivo*. Thus, N-glycan modification controls cytokine receptor–mediated functions. *PTL*

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