Itchy death

Tumor necrosis factor (TNF) induces cell survival and death signals via the transcription factor NF-κB and Jun kinase (Jnk) pathways, respectively. In *Cell*, Karin and colleagues evaluate how activation of the Jnk cell death pathway negatively regulates c-FLIP$_L$, which normally inhibits caspase-8 activation and cell death. They find that injection of mice with a potent Jnk pathway inducer causes inactivation of c-FLIP$_L$ and apoptosis. Jnk-mediated inhibition of c-FLIP$_L$ occurs indirectly via activation of the E3 ubiquitin ligase Itch, which ubiquitinates cFLIP$_L$, marking it for degradation. Cells lacking Itch or Jnk do not inhibit c-FLIP$_L$ and are protected from apoptosis. Jnk-induced Itch–c-FLIP$_L$ interaction is confirmed biochemically and is required for apoptosis-associated liver damage *in vivo*. The identification of Itch as a key regulator of c-FLIP$_L$ adds to the regulatory scheme of important TNF-Jnk signaling pathways. ***DCB***

***Cell* 124, 601–613 (2006)**

Identifying NFAT regulators

Calcium mobilization results in dephosphorylation and nuclear translocation of NFAT transcription factors. In the nucleus, the kinases CK1 and GSK3 rephosphorylate and induce nuclear export of NFAT. In *Nature*, Rao and colleagues use a genome-wide RNA interference screen in drosophila to identify the cytoplasmic and nuclear NFAT kinases DYRK2 and DYRK1A, respectively. 'Knockdown' of DYRK2 allows calcium-independent NFAT nuclear translocation, and overexpression of DYRK2 prevents calcium-induced NFAT dephosphorylation and nuclear translocation. DYRK2-mediated phosphorylation of the NFAT regulatory domain SP3 motif enhances subsequent GSK3- and CK1-mediated NFAT phosphorylation. In the cytoplasm, DYRK2 might maintain basal NFAT phosphorylation in unstimulated cells, whereas in the nucleus, DYRK1A might 'prime' NFAT for later phosphorylation by GSK3 or CK1. These data emphasize the potential utility of drosophila small interfering RNA screens for identifying evolutionarily conserved regulators of mammalian signaling pathways. *CB*

Nature (1 March 2006) doi:10.1038/nature04631

IL-2 paradox

Memory CD8$^+$ T cells have high expression of interleukin 2 receptor-β (IL-2Rβ), which is required for IL-2 and IL-15 responsiveness and survival *in vivo*. In *Science*, Sprent and colleagues resolve the paradox that stimulation of memory CD8$^+$ T cell proliferation *in vivo* occurs after treatment with either IL-2 or with antibody to IL-2 (anti-IL-2), thought to deplete IL-2. Because anti-IL-2 does not cause memory CD8$^+$ T cell proliferation in IL-2-deficient mice, the authors propose that anti-IL-2 mediates stimulation by forming immune complexes with endogenous IL-2. Support for that conclusion is provided by *in vitro* immune assays comparing various IL-2 monoclonal antibodies, not all of which stimulate CD8$^+$ T cell proliferation. A similar stimulator effect is seen with IL-4–anti-IL-4 and IL-7–anti-IL-7. The exact mechanism by which IL-2–anti-IL-2 immune complexes promote memory CD8$^+$ T cell proliferation is not clear, but the therapeutic implications for augmenting memory CD8$^+$ T cell numbers by this method are apparent. *DCB*

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Research notes written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey.

T$_H$-17 differentiation

The mechanisms regulating development of the IL-17–producing CD4$^+$ T helper lineage (T$_H$-17) are not understood. In *Immunity*, Stockinger and colleagues demonstrate that T$_H$-17 differentiation requires both pro- and anti-inflammatory components. IL-6 secreted by Toll-like receptor–stimulated dendritic cells and transforming growth factor-β secreted by regulatory T cells are sufficient to induce T$_H$-17 differentiation from naive CD4$^+$ T cells *in vitro*. Although neither necessary nor sufficient for T$_H$-17 differentiation, IL-23 supports the growth and survival of T$_H$-17 cells. T$_H$-17 cells differentiated *in vitro* do not express transcription factors essential for the development of T$_H$1 cells (T-bet and Hlx) or T$_H$2 cells (GATA-3), solidifying the idea that IL-17-producing T cells constitute a distinct T$_H$ lineage. These results might provide insight into previously puzzling reports of both pro- and anti-inflammatory functions for IL-17 and transforming growth factor-β. *CB*

Immunity **24**, 179–189 (2006)

CD95 internalization

Peripheral lymphocyte homeostasis is regulated in part by the death receptor Fas (also called CD95). Receptor activation and internalization induced by interaction with CD95 ligand (FasL) can trigger cellular apoptosis. In the *EMBO Journal*, Lee *et al.* show that internalization of activated CD95 is crucial for assembly of the caspase-rich death-inducing signaling complex (DISC). Endosomes containing CD95 recruit Fas-associated death domain (FADD) and caspase-8 to initiate the death signal. Apoptosis is inhibited when CD95 internalization is blocked. Instead, signaling by surface CD95, achieved by multiple experimental strategies, leads to activation of NF-κB and the kinase Erk and the induction of prosurvival signals. These data suggest that endosomal localization is required for efficient unmasking of the CD95 death domain and subsequent proapoptotic signaling mediated through DISC. Whether such nonapoptotic CD95 signaling occurs in more physiological settings remains to be shown, but such signals might explain resistance to CD95 ligand–mediated cell death. *LAD*

EMBO J. (23 February 2006) doi:10.1038/sj.emboj.7601016

Cellular transcytosis

Extravasating leukocytes are thought to cross endothelial barriers by passing through cellular junctions. In *Nature Cell Biology*, Millán *et al.* show that lymphocytes can pass through endothelial cells by a process called 'transmigration'. Endothelial cells activated with TNF could form channels lined by the adhesion molecule ICAM-1 that result from cytoskeletal reorganization of F-actin and caveolin 1. ICAM-1 is transported via caveolar vesicles to the underlying basal surfaces of the activated endothelial cells. Such channels, which are ringed by caveolin 1, are capable of forming at sites of interaction with arrested T lymphocytes. By extending pseudopodia into these channels, T cells could initiate transmigration through the activated endothelium. The relative contribution of such channel formation and subsequent transcytosis, rather than junctional diapedesis, in mediating leukocyte access to underlying tissues remains controversial. ***LAD***

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