Directing apoptotic cell clearance

Macrophages engulf apoptotic cells to prevent immune responses to self antigens. In *Nature Medicine*, Chawla and colleagues show that PPAR-δ, a sensor of fatty acids, is essential for efficient macrophage phagocytosis of apoptotic cells. Apoptotic cells trigger PPAR-δ expression in macrophages, and *Ppard*$^{-/-}$ macrophages inefficiently clear apoptotic cells *in vitro* and *in vivo*. *Ppard*$^{-/-}$ mice have lower serum concentrations of opsonins, and wild-type serum or a purified form of the opsonin C1qb restores apoptotic cell engulfment by *Ppard*$^{-/-}$ macrophages. In a manner dependent on PPAR-δ, apoptotic cells boost expression of opsonins and interleukin 10 (IL-10) and suppress expression of IL-12p40 and tumor necrosis factor (TNF). Mice lacking PPAR-δ systemically or exclusively in macrophages are more susceptible to lupus-like diseases. Thus, the fatty acids released by apoptotic cells drive further optimization of the engulfment response. ***CB***

***Nat. Med.* (18 October 2009) doi:10.1038/nm.2048**

One more way to be suppressive

IL-10 exerts its anti-inflammatory effect through direct transcriptional control of cytokine expression as well as indirect modulation of the costimulatory properties of antigen-presenting cells. In the *Proceedings of the National Academy of Sciences*, Chang *et al.* describe the ubiquitination and subsequent degradation of the MyD88–dependent signaling molecules IRAK4 and TRAF6 as an additional mechanism that controls the production of proinflammatory cytokines. IL-10 alone is not sufficient to induce these effects. Intact MyD88 is required for IRAK4 and TRAF6 ubiquitination and degradation, which suggests that MyD88 pathway stimulation may be needed to trigger the recruitment and function of E3 ubiquitin ligases and/or activation of the proteasome. These observations add another regulatory circuit to the multiple levels of negative control targeting Toll-like receptor signaling. *IV*

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Viral entrapment

Viral dissemination requires the release of newly synthesized virions from hijacked cells. In *Cell*, Bieniasz and colleagues report how tetherin, an interferon-inducible protein, blocks the release of HIV and other enveloped viruses. Tetherin contains an N-terminal transmembrane domain, a central coiled-coil protein-dimerization domain and a C-terminal GPI-linked anchor domain, which collectively form a double-lobed structure with two membrane-attachment sites. An artificial composite tether made of a chimeric protein using these three domains can also block viral release. This artificial construct, unlike native tetherin, is not inhibited by the HIV Vpu protein. Both anchors allow the incorporation of tetherin into viral particles, but only the transmembrane domain of native tetherin is sensitive to Vpu-mediated inhibition. These findings suggest ways to inhibit viral release. ***LAD***

***Cell* 139, 499–511(2009)**

Written by Christine Borowski, Laurie A. Dempsey & Ioana Visan

Healing powers

Chronic or unresolved inflammation can lead to tissue damage or, during sepsis, to death. In *Nature*, Serhan and colleagues characterize a potent anti-inflammatory molecule, resolvin D2, which is naturally produced by the metabolism of omega-3 fatty acids. Resolvin D2 decreases neutrophil infiltration, ROS generation and proinflammatory cytokine production while recruiting macrophages and enhancing their phagocytic activity. Resolvin D2 acts via a pertussis toxin–sensitive G protein–coupled receptor (GPCR) whose identity remains unknown. Also in *Nature*, Mackay and coworkers show that short-chain fatty acids produced by gut bacteria binds to another GPCR, GPR43, to limit inflammatory processes. Mice lacking GRP43 develop more-severe colitis and other inflammatory diseases. Germ-free wild-type mice also experience severe colitis that can be treated by the addition of acetate or fermentative bacteria and fiber to the diet to provide short-chain fatty acids. Whether the resolvin D2 and GRP43 pathways intersect remains unknown. *LAD*

Nature **461**, 1282–1286 & 1287–1291 (2009)

Remote-controlled activation

The use of the circulatory system to deliver extracellular signals to distant targets is well known, especially for signals secreted in large quantities, such as hormones. In the *Journal of Experimental Medicine*, Kunder *et al.* show that peripheral mast cells use submicrometer heparin-based particles to deliver TNF to draining lymph nodes. These insoluble, stable particles protect TNF from dilution and degradation and are able to traffic through the lymphatic system to the lymph node sinuses, where they become sequestered. Minute amounts of TNF, if packaged in particles, can induce lymph node hypertrophy at physiological concentrations when administered to mice. This observation suggests that such a long-distance communication system may be important in early inflammation, when only small amounts of pre-stored mediators are available. The mechanisms of signal release, once the particles reach the lymph node, remain to be elucidated. ***IV***

***J. Exp. Med.* (5 October 2009) doi:10.1084/jem.20090805**

Granule-polarization pathways

CTL-mediated target cell killing requires polarization of the microtubule-organizing center (MTOC) and cytotoxic granules toward the target cell interface. In *Immunity*, groups led by Griffiths and Sykulev shed light on the molecular basis of the observation that the strength of TCR signals is proportional to the efficiency of CTL-mediated killing. Griffiths and co-workers find that weaker TCR agonists induce substantial MTOC polarization but less accumulation of phosphorylated Src and Erk kinases and cytotoxic granules at the CTL–target cell interface. Sykulev and colleagues find that although strong TCR agonists drive granules toward the secretory domain at the cSMAC, weaker TCR agonists route granules along a slower and more circuitous route through the pSMAC. Forcibly slowing calcium accumulation in CTLs stimulated with strong agonists drives granules toward the pSMAC. Together these reports indicate that granule rather than MTOC polarization varies with the strength of TCR signaling. *CB*

Immunity **31**, 621–631 & 632–642 (2009)