RIG-I in bacterial clearance

The cytosolic protein RIG-I is best known as an intracellular viral sensor that triggers the expression of interferon and proinflammatory genes. In *Cell Host & Microbe*, Kong *et al.* show that RIG-I acts together with Toll-like receptors (TLRs) to enhance macrophage clearance of invading bacteria. RIG-I facilitates F-actin polymerization in membrane lamellipodia after TLR stimulation or contact with bacteria. RIG-I-deficient macrophages show less phagocytic uptake of bacteria and less actin polymerization in response to TLR signaling. RIG-I interacts with F-actin via its C-terminal helicase domain and participates in the nucleation complex of Arp2/3 and the GTPases Cdc42 and Rac1 that initiate the actin-polymerization process. RIG-I-deficient mice are more susceptible to infection by *Escherichia coli* and have higher bacterial loads despite proper recruitment of neutrophils and macrophages to infected tissues. How TLR signals trigger this RIG-I-mediated phagocytic response remains to be elucidated. ***LAD***

Cell Host Microbe **6, 150–161 (2009)**

Integrating 'exit' signals

Mst1 is a protein kinase essential for clustering of the integrin LFA-1, cell polarization and adhesion induced by Rap1-RAPL. In the *Journal of Immunology*, Dong *et al.* show that Mst1 has a cell-intrinsic role in controlling thymocyte egress. Mst1-deficient mice have considerably fewer peripheral T lymphocytes, partially due to impaired homing to peripheral lymphoid organs; this defect is independent of the survival of naive T cells. In addition, more $CD62L^{hi}CD69^{lo}$ mature single-positive thymocytes accumulate in the thymus, and tracing of recent emigrants shows defective thymocyte output in the circulation. Mst1 deficiency does not influence cell migration in response to signals by sphingosine 1-phosphate but severely impairs CCR7-mediated chemotaxis, which shows that Mst1 signaling and chemokine-triggered integrin polarization are important for thymic egress. *IV*

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Regulation by redox

Cysteine is an essential amino acid, yet naive T cells are unable to efficiently use its more abundant oxidized form, cystine. In *Nature Chemical Biology*, Banerjee and colleagues report that dendritic cell (DC) interaction provides extracellular cysteine to naive T cells, which is necessary for T cell proliferative responses. Extracellular cystine is taken up by the x_c^- transporter, whose expression in DCs is enhanced by interaction with naive T cells. Intracellular cystine is subsequently reduced and incorporated into glutathione, which itself is exported and metabolized extracellularly to provide cysteine to interacting effector T cells. The cystine-cysteine redox pathway requires activation of the transcription factor NF-κB in the DCs. Regulatory T cells (T_{reg} cells) intercede in this redox pathway, blocking DC elaboration of extracellular cysteine and reducing intracellular glutathione accumulation in effector T cells interacting with the DCs, which leads to less T cell proliferation. How glutathione metabolism is regulated by the DC–T_{reg} cell interaction remains unknown. ***LAD***

Nat. Chem. Biol. **(30 August 2009) doi:10.1038/nchembio.212**

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Another switch found

Originally identified as a 'decision maker' during B cell terminal differentiation, Blimp-1 has been subsequently described as being important in T cell homeostasis. In *Immunity*, three different groups led by Kaech, Nutt and Wherry further demonstrate that Blimp-1 promotes the differentiation of terminal short-lived cytotoxic T cells rather than the formation of long-lived central memory $CD8^+$ T cells. In the absence of Blimp-1, effector $CD8^+$ T cells lose expression of cytolytic molecules and acquire an expression profile similar to that of memory cell precursor cells, with higher expression of the transcription factors Bcl-6 and Eomes, as well as enhanced survival, proliferative capacity and interleukin 2 (IL-2) production. In addition, Blimp-1-deficient $CD8^+$ T cells fail to downregulate the chemokine receptor CCR7, which leads to more retention in the lymphoid organs and less migration to peripheral tissues. Very little is known so far about the 'upstream' signals that regulate Blimp-1 expression in T cells. *IV*

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'Find me' in the thymus

Even in organs such as the thymus, in which large numbers of cells die at developmental checkpoints, apoptotic cells are rapidly cleared by phagocytosis. In *Nature*, Ravichandran and co-workers identify a chemoattractant 'find me' signal sent by apoptotic cells and received by monocytes and macrophages. Supernatants of apoptotic thymocytes contain a heat-stable soluble factor able to recruit monocytes *in vitro* and *in vivo*. Hydrolysis of nucleoside triphosphates and diphosphates by the enzyme apyrase neutralizes this chemoattractant activity of apoptotic cell supernatants. The nucleoside triphosphates ATP and UTP are present in supernatants of apoptotic but not live cells and are sufficient on their own to attract monocytes. Inhibition or lower expression of the G protein coupled–receptor $P2Y_2$ in monocytes results in less migration toward apoptotic cell supernatants and impairs clearance of apoptotic thymocytes *in vivo*. Thus, by releasing nucleotides that stimulate $P2Y_2$ on phagocytes, apoptotic cells facilitate their own clearance. ***CB***

Nature **(10 September 2009) doi:10.1038/nature08296**

Eos enables suppression

The transcription factor Foxp3 represses the expression of select proinflammatory genes in T_{reg} cells. In *Science*, Pardoll and co-workers find that the zinc-finger Ikaros family transcription factor Eos is essential for Foxp3-mediated gene silencing in mouse T_{reg} cells. Eos has higher expression in $Foxp3^+$ $CD4^+$ T cells than in $Foxp3^-$ $CD4^+$ T cells. Foxp3 and Eos physically interact in T_{reg} cells, and this interaction is essential for Foxp3-induced suppression of expression of the gene encoding IL-2 (*Il2*). Eos recruits C-terminal–binding protein 1 (CtBP1) to Foxp3 and the *Il2* promoter, and both Eos and CtBP1 are essential for the maintenance of repressive histone modifications and DNA methylation at the *Il2* promoter in T_{reg} cells. In the absence of Eos, many genes normally suppressed by Foxp3 are derepressed. Eos-specific small interfering RNA results in lower suppressive activity of and actually induces some pathogenic activity in T_{reg} cells in a mouse model of colitis. *CB*

Science (20 August 2009) doi:10.1126/science.1176077