Compartmentalizing cross-presentation

By cross-presenting internalized proteins on major histocompatibility complex (MHC) class I molecules, dendritic cells facilitate the priming of $CD8^+$ T cells to antigens derived from transformed and pathogen-infected cells. In *Science*, van Endert and colleagues document a function for the aminopeptidase IRAP in cross-presentation. Like the endoplasmic reticulum aminopeptidases ERAP1 and ERAP2, IRAP trims precursor peptides to generate MHC class I–binding epitopes. Interferon-γ stimulation increases IRAP1 abundance. IRAP colocalizes with early but not late phagosomes and with compartments containing internalized MHC class I molecules but not with LAMP-1^+ MHC class II–containing vesicles. Although it is dispensable for the presentation of endogenous protein on MHC class I molecules, IRAP is essential for optimal cross-presentation of internalized protein. As ERAP enzymes also contribute to cross-presentation, IRAP and ERAP aminopeptidases may act in distinct cross-presentation pathways. ***CB***

Science **(4 June 2009) doi:10.1126/science.1172845**

Feedback for pDCs

Plasmacytoid dendritic cells (pDCs) sense nucleic acids through Toll-like receptor 7 (TLR7) and TLR9 and produce copious amounts of type I interferons. In the *Journal of Experimental Medicine*, Cao *et al.* identify bone marrow stromal cell antigen 2 (BST2) as a natural ligand for the inhibitory receptor ILT7 expressed by pDCs and signals a halt to proinflammatory gene expression. BST2 is induced by interferon and specifically interacts with ILT7 to blunt interferon expression induced by TLR signaling in pDCs. Thus, BST2-ILT7 functions as a negative feedback circuit to limit excessive interferon production. ILT7 signals through the ITAM-containing adaptor FcεR1γ, but how this pathway inhibits TLR signaling remains unknown. Because many tumor cell lines express BST2, the BST2-ILT7 interaction might allow tumors to escape innate immunity, making this interaction a potential target for therapeutic intervention. *LAD*

J. Exp. Med. (29 June 2009) doi:10.1084/jem.20090547

IL-33: the odd one out

Whether interleukin 33 (IL-33) requires proteolysis by inflammatory caspases for activation, similar to other IL-1 family members, is unclear. In *Immunity*, Martin and colleagues find that the inflammatory caspases 1, 4 and 5 are actually not required for IL-33 proteolysis. Instead, IL-33 proteolysis requires caspases activated during apoptosis (caspases 3 and 7). However, IL-33 does not need proteolytic processing to activate the transcription factor NF-κB or for binding to its receptor, ST2. The caspase-cleaved form, but not the uncleaved form, of IL-33 shows impaired proinflammatory activity *in vitro* and *in vivo*. Only during necrosis is IL-33 secreted in an uncleaved form. IL-33 therefore does not require proteolysis for activation but instead loses its bioactivity through cleavage. This may serve to dampen the proinflammatory properties of IL-33 that would otherwise ensue during apoptosis. ***JDKW***

Immunity **(25 June 2009) doi:10.1016/j.immuni.2009.05.007**

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Immune role for 'eyes absent'

Undigested DNA from apoptotic cells or some viruses triggers a 'danger' signal that is detected by cytosolic non-Toll-like receptors, which prompts macrophages to secrete tumor necrosis factor, interferon-β and the chemokine CXCL10. In *Nature*, Nagata and colleagues show that the phosphatase EYA4 (eyes absent 4) activates a DNA-sensing 'danger' response. EYA4 associates with the cytosolic nucleic acid–sensor complex composed of IPS-1 (MAVS), STING and NLRX1. EYA4 has both phosphotyrosine and phosphothreonine phosphatase activity, but only the latter activity triggers interferon-β expression by a pathway that requires the transcription factors IRF3 and IRF7. The relevant phosphothreonine targets of EYA4 remain unknown, but the identification of an activating phosphatase suggests that the IPS-1 signaling complex itself is negatively regulated by kinase action. *LAD*

Nature (28 June 2009) doi:10.1038/nature08138

Another suppressive mediator

Regulatory T cells (T_{reg} cells) can suppress T cell proliferation through the cell surface molecules CTLA-4 and GITR and by the secretion of immunosuppressive cytokines such as IL-10 and TGF-β. In the *Proceedings of the National Academy of Sciences*, Bachmann and colleagues identify secreted phospholipase A2–HD (sPLA2-HD) as an additional soluble mediator of T_{reg} cell suppression. T_{reg} cells have higher expression of sPLA2-HD than do non–T_{reg} cells or classical effector T cells. Also, sPLA2-HD suppresses T cell proliferation *in vitro* and *in vivo*. Suppression does not require the catalytic domain of sPLA2-HD. Moreover, sPLA2-HD induces T_{reg} differentiation *in vitro*, and this correlates with an attenuated PI(3)K-Akt-mTor pathway. Notably, administration of sPLA2-HD could interfere with two mouse models of autoimmunity: EAE and colitis. The receptor by which sPLA2-HD mediates its suppressive effects on T cells has yet to be identified. ***JDKW***

Proc. Natl. Acad. Sci. USA **(29 June 2009) doi:10.1073/pnas.0812569106**

Gut homeostatic loop

In several organisms, intestinal epithelial cells (IECs) that die naturally or are damaged by infection or stress are replaced, presumably by intestinal progenitor cells. Using the drosophila midgut as a model of intestinal epithelium, in *Cell* Edgar and colleagues explain how IECs direct their own replacement during homeostasis and infection. Activation of the kinase Jnk in or apoptosis of absorptive enterocytes, a type of IEC, results in mitosis of intestinal stem cells (ISCs) in a way dependent on the production of Unpaired IL-6-like cytokines and on signaling by the kinase Jak and STAT transcription factors in ISCs. Enterocyte apoptosis also induces expression of the Notch ligand Delta, which is dispensable for ISC proliferation but is essential for enterocyte differentiation. Flies lacking STAT or Notch in ISCs show impaired enterocyte renewal and died after infection with the Gram-negative bacterium *Pseudomonas entomophila*. Thus, cytokines relay information about enterocyte status to ISCs and thereby facilitate dynamic enterocyte renewal. *CB*

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