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Evading NKG2D

Noncoding microRNAs (miRNAs) bind to 3′ untranslated regions and suppress the translation and/or induce degradation of mRNA transcripts. In *Science*, Mandelboim and colleagues identify a viral miRNA as another immunoevasion strategy used by human cytomegalovirus (HCMV). The miRNA hcmv-*miR-UL112* binds to and inhibits the translation of the transcript encoding MICB, the stress-induced ligand of the NKG2D-activating receptor whose function is also suppressed post-translationally by the HCMV protein UL16. Intact hcmv-*miR-UL112* is essential for HCMV-induced reductions in MICB expression. Cells infected with HCMV strains expressing mutated hcmv-miR-UL112 are more susceptible to NKG2D-dependent natural killer cell–mediated cytotoxicity than are cells infected with wild-type HCMV. These findings indicate that HCMV can use many strategies to evade NKG2D-mediated recognition. Whether other viruses use similar potentially redundant immunoevasion mechanisms is not yet clear. ***CB***

***Science* 317, 376–381 (2007)**

pDC priming ability

Plasmacytoid DCs (pDCs) produce large quantities of type I interferon and provide costimulatory signals to conventional DCs (cDCs) and natural killer cells, but whether pDCs, like cDCs, can stimulate naive T cells *in vivo* remains unclear. In the *Journal of Experimental Medicine*, Jung and coworkers show that pDCs in lymph nodes, but not in the spleen, can stimulate antigen-specific $CD4^+$ but not $CD8^+$ T cell responses. $CD4^+$ T cells in lymph nodes proliferate and produce interferon-γ after antigen injection even in mice with genetic ablation of cDCs, B cells or Langerhans cells. Lymph node $CD4^+$ T cells also proliferate after injection of antigen specifically targeted to pDCs, and pDCs in the draining lymph nodes ingest and process antigen injected into footpads. The molecular basis of the apparent T cell lineage–specific and organ-specific T cell–stimulatory capacity of pDCs remains to be identified. *CB*

J. Exp. Med. (23 July 2007) doi:10.1084/jem.20062373

DC integrin activates TGF-β

TGF-β, a central mediator of many immune and nonimmune activities, is secreted in an inactive form as a procytokine. In *Nature*, Sheppard and colleagues find that expression of integrin $\alpha_v\beta_8$ on dendritic cells (DCs) is important for the conversion of TGF-β to its active form. Like other integrins, including epithelial cell–specific $\alpha_v\beta_6$, $\alpha_v\beta_8$ has been shown to activate TGF-β; however, mice lacking $\alpha_v\beta_8$ die shortly after birth, and thus the systemic effects of $\alpha_v\beta_8$ deletion have remained unknown. Sheppard and colleagues show that after conditional deletion of $\alpha_v\beta_8$ from either T cells or DCs, mice lacking DC-expressed $\alpha_v\beta_8$ have much less TGF-β activation and suffer severe colitis and autoimmunity. In addition, induction of T_{reg} cells in the colon, but not the spleen, is lower in such mice. These data indicate that DC-expressed $\alpha_v\beta_8$ is essential for the TGF-β activation required for the induction of T_{reg} cells. ***DCB***

***Nature* (12 August 2007) doi:10.1038/nature06110**

New role for IL-15

Secreted IL-15 has many functions in immune cell activation and homeostasis. In *Nature Medicine*, Bulfone-Paus and colleagues identify a role for intracellular IL-15 in regulating mast cell function. IL-15–deficient mice show increased survival in sepsis models because of more neutrophil recruitment and bactericidal activity. Mast cell–deficient mice reconstituted with bone-marrow–derived *Il15*$^{-/-}$ mast cells likewise show increased survival. Mice lacking the IL-15 receptor do not share this phenotype, which suggests that secreted IL-15 is not responsible for this phenomenon. Mast cells lacking IL-15 synthesize and secrete more MCP-2, a chymase that activates neutrophil-recruiting chemokines. Transfection experiments show that intracellular IL-15 decreases *Mcpt2* expression but not MCP-2 protein activity. How intracellular IL-15 negatively regulates *Mcpt2* expression is yet to be elucidated. *LAD*

Nat. Med. (22 July 2007) doi:10.1038/nm1615

Trans IL-6 suppresses T_{reg} cells

The cytokine interleukin 6 (IL-6) is a pleiotropic factor that has both proinflammatory and anti-inflammatory effects. In the *Journal of Immunology*, Becker and colleagues demonstrate that IL-6 *trans*-stimulation of T cells, which occurs when the complex of IL-6 and soluble IL-6 receptor (IL-6R) binds to gp130 (the third component of this signaling complex), abrogates the development of $Foxp3^+$ regulatory T cells (T_{reg} cells) from naive $CD4^+CD25^-$ precursor cells. Using a recombinant fusion protein (HIL-6) consisting of IL-6 and the portion of IL-6R shown before to be sufficient for *trans*-signaling, the authors show that stimulation of naive $CD4^+CD25^-$ T cells with HIL-6 plus antibodies to CD3 and CD28 completely blocks the development of $Foxp3^+$ T_{reg} cells. *In vivo*, adoptive transfer of HIL-6–treated T cells results in loss of colitis suppression. 'Hyperinduction' of the transforming growth factor-β (TGF-β) inhibitor Smad7 correlates with lower $Foxp3^+$ expression in HIL-6–treated T cells. IL-6 *trans*-signaling, therefore, is a potent inhibitor of the development of $Foxp3^+$ T_{reg} cells. ***DCB***

***J. Immunol.* 179, 2041–2045 (2007)**

Early AID

Immunoglobulin class switching and somatic hypermutation require activation-induced cytidine deaminase (AID), an enzyme first identified in germinal center B cells. In *Immunity*, Han *et al.* show expression of AID in developing pre–B cells and immature B cells that reside in the bone marrow of replete wild-type mice. Evidence for both ongoing variable-region mutation and isotype switching is present in purified bone marrow cells. Mice lacking Blimp-1 (and thus lacking plasma cells) and athymic mice also show early B cell expression of AID. But mice deficient in the signaling molecules MyD88 or Btk and the '3D' mouse, which has impaired Toll-like receptor signaling, all have lower bone marrow expression of AID. Thus, these results show that AID contributes to the diversification of mouse immunoglobulin genes at earlier steps in B cell ontogeny than previously thought. *LAD*

Immunity **27**, 64–75 (2007)

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