A matter of life and death

The serine-threonine kinase RIPK1 regulates not only cell survival mediated by induction of the transcription factor NF-κB but also cell death by inducing apoptosis or necroptosis. In *Nature*, Takahashi *et al.* show that RIPK1 suppresses caspase 8-dependent apoptosis but not RIPK3-dependent necroptosis in intestinal epithelial cells. Mice with conditional deletion of RIPK1 in the gut epithelium undergo massive and lethal death of intestinal epithelial cells and intestinal inflammation dependent on bacterial colonization and signaling through TLRs and the receptor TNFR1. Deletion of caspase-8 completely 'rescues' the apoptosis of intestinal epithelial cells in RIPK1-deficient mice, but deletion of TNFR1 does not. Moreover, TNF-induced activation of NF-κB is intact in RIPK1-deficient cells. Thus, RIPK1 deficiency sensitizes the intestinal epithelium to TNF-induced, caspase 8-mediated apoptosis independently of defects in NF-κB activation, which suggests a prosurvival role for RIPK1 in these cells. ***IV***

***Nature* 513, 95–99 (2014)**

NF-κB flavors in germinal centers

NF-κB has a critical role in germinal center (GC) lymphomagenesis. In *The Journal of Experimental Medicine*, Klein and colleagues use mice with conditional deletion of genes encoding the canonical NF-κB subunits c-Rel and RelA in activated B cells to show that these two subunits have distinct functions at different developmental stages during the GC B cell reaction. RelA is not required for GC formation or affinity maturation but is necessary for the differentiation of GC B cells into plasmablasts. RelA-deficient B cells do not upregulate the transcription factor Blimp-1, which is required for the generation of plasma cells. In contrast, c-Rel is dispensable for plasma cell differentiation but is required for the maintenance of GC B cells though control of a metabolic program required for growth of these rapidly proliferating cells and their entry into the cell cycle. Thus, canonical NF-κB controls the GC B cell reaction through distinct and nonredundant mechanisms. *IV*

J. Exp. Med. (1 September 2014) doi:10.1084/jem.20132613

Isoketals drive hypertension

Isoketals are highly reactive oxidation products of arachidonic acid that can form adducts with cellular proteins. In the *Journal of Clinical Investigation*, Harrison and colleagues link the production of isoketals to stimulation of the immune system and hypertension. Dendritic cells (DCs) in an angiotensin-induced model of mouse hypertension show signs of oxidative stress and develop enrichment for isoketals. The isoketals in these DCs generate neoantigens, which can be recognized by T cells as non-self. In addition, the isoketal-containing DCs upregulate the costimulatory molecules CD80 and CD86, as well as the cytokines IL-6 and IL-23, and therefore efficiently activate T cells to proliferate and produce proinflammatory cytokines. Chemical inhibition of isoketal activity not only prevents the stimulation of the immune system but also ameliorates the hypertension in this model. These findings therefore suggest new ways of modulating the pathological activation of the immune system that results from oxidative damage. ***ZF***

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Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Human T cell variations

Genome-wide association studies have been informative in identifying potential genetic contributions in various immune system–related diseases, but the abundance of variation in the expression of genes of the immune system in healthy human populations has remained unknown. In *Science*, Benoist and colleagues report natural variations in gene expression that occur when $CD4^+$ T cells are activated. They obtained resting T cells from 348 people of varying ethnicity and profile their genome-wide expression after stimulation under neutral or T_H17-polarizing conditions. By subsequent nanostring analysis, they determine the molecular abundance of 236 transcripts with the greatest intersubject variance across the donor population. They find variance in the overall response to T cell stimulation, for which inherited *cis* regulatory loci determine approximately 25% of the observed variance and which could be mapped to expression quantitative trait loci. In particular, differences in expression of the gene encoding the α-chain of the receptor for IL-2 could be attributed to distinct allele variants that differ by two nucleotides and that alter binding of the transcription factor YY1. This demonstrates that such changes may have a profound effect on immunity. *LAD*

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Tetherin signaling

Tetherin is an interferon-inducible host protein that not only prevents the release of membrane-enveloped virus particles but also triggers activation of NF-κB to elicit the production of proinflammatory cytokines that alert neighboring cells. In *Cell Host & Microbe*, Neil and colleagues reveal that Tyr6 in the Src-homology 2 motif YDYCRV, present in the cytoplasmic tail, becomes phosphorylated during viral budding and activates Syk-TRAF2,TRAF6-TAK1 signaling pathways. Although Tyr6 is not needed for blockade of virion release, phosphorylation of tetherin is triggered by retention of virions at the plasma membrane. Tetherin is linked to the actin cytoskeleton via the Rac-GAP protein RICH2, which promotes clustering of tetherin during viral budding. This proximity in turn leads to Src kinase–mediated phosphorylation of tetherin tyrosine to initiate the intracellular signaling cascade. Notably, this tetherin cytoplasmic tail is subject to intense evolutionary pressure as viruses attempt to evade tetherin-mediated restriction. ***LAD***

***Cell Host Microbe* 16, 291–303 (2014)**

Decrepit DCs

Aging is associated with dysfunction of the immune system at various levels. In the *Proceedings of the National Academy of Sciences*, Strominger and colleagues demonstrate that aging also impairs the ability of DCs to prime NK cells. DCs obtained from aged mice and stimulated with the RNA duplex poly(I:C) are ineffective at activating NK cells or priming their ability to respond to tumors. This dysfunction seems to be DC intrinsic because NK cells from aged mice are essentially normal in their responsiveness when primed by DCs from young mice. The impaired function of DCs from aged mice is a consequence of their lower expression of factors required for the priming of NK cells, such as the cytokines IL-15 and IL-18 or the plasma membrane molecule CD48. These data offer mechanistic insights into the age-related enhanced susceptibility to viruses and cancer. *ZF*

PNAS (15 September 2014) 10.1073/pnas.1414780111