NLRX1 negatively regulates STING

Cytosolic infection with DNA viruses triggers innate immune responses via the STING adaptor pathway, which activates the kinase TBK1 and transcription factors IRF3 and NF-κB to produce type I interferons. In *Cell Host & Microbe*, Guo *et al.* report that the Nod-like receptor NLRX1 is a negative regulator of STING. NLRX1-deficient cells express more type I interferons after infection with the retrovirus HIV-1 or treatment with cyclic GAMP or cyclic di-GMP, which activate STING-dependent responses. NLRX1 seems to block the interaction of STING with TBK1, which prevents downstream activation. Given that NLRX1 is localized to mitochondrial membranes, whereas STING is tethered to the endoplasmic reticulum, the kinetics of their interaction and how these proteins come into promixity still need to be determined. Nevertheless, interfering with NLRX1's activity might enhance anti-viral responses, including those directed against HIV-1. ***LAD***

***Cell Host Microbe* 19, 515–528 (2016)**

DCs regulate T_{FH} generation

Follicular helper T cells (T_{FH} cells) contribute to germinal-center reactions to promote plasma-cell generation and antibody affinity maturation. In *Nature*, Cyster and colleagues identify a regulatory role for $CD4^+$ dendritic cells (DCs) in T_{FH} differentiation. Naive $CD4^+$ T cells upregulate their expression of EBI2, a G-protein-coupled receptor, after immunization or *in vitro* activation. EBI2 directs migration to the B cell–T cell interface and interaction with antigen-presenting $CD4^+$ DCs. EBI2-deficient T cells proliferate less and form fewer T_{FH} cells than do wild-type T cells. Interestingly, activated $CD4^+$ DCs express the cytokine receptor CD25, which limits the availability of interleukin 2 (IL-2). This sequestration of IL-2 favors T_{FH} differentiation over differentiation into the T_H1 subset of helper T cells. Specific loss of CD25 expression in DCs likewise leads to defective generation of T_{FH} cells. These findings show that DC–T cell interactions are more complex and involve feedback regulation that influences T cell polarization. *LAD*

Nature (5 May 2016) doi:10.1038/nature17947

Charting disease space

'Resilience' refers to the ability of any system to return to its original state, and in the case of infectious disease, this determines whether an organism recovers from infection or undergoes catastrophic collapse. In *PLoS Biology*, Schneider and colleagues monitor changes in multiple biological parameters after malarial infection of mice to predict the outcome of infection. At the outset of infection, it is not possible to predict whether a given mouse will die or recover, but plotting the trajectories of two given parameters through time (such as the number of erythrocytes versus that of natural killer cells) often leads to the formation of a looped relationship known as 'hysteresis'. A tight loop describes a resilient organism, whereas organisms fated to die trace a wider loop. By monitoring the trajectories of specific parameters in patients and without any *a priori* knowledge of the time of infection, it might be possible to predict the severity of symptoms and prioritize medical interventions. ***ZF***

***PLoS Biol.* (18 April 2016) doi:10.1371/journal.pbio.1002436**

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

Neonatal sepsis

The proinflammatory cytokine IL-18 is elevated in both normal neonates and those with sepsis, in whom it has a deleterious role. In the *Proceedings of the National Academy of Sciences USA*, Moore and colleagues use a neonatal mouse model of polymicrobial sepsis to investigate the mechanistic basis of IL-18's function in sepsis. IL-18-deficient mice are resistant to sepsis, and exogenous supply of this cytokine worsens the outcome of sepsis, increases the bacterial load in the peritoneum and manifests as damage to the gut ileum. Mechanistically, IL-18 activates secretion of the proinflammatory cytokine IL-17A by γδ T cells, and it is this that worsens symptoms in this model of sepsis. These data reveal an unexpected pathway involved in the pathology of neonatal sepsis and might lead to new drug targets in this otherwise nearly intractable condition. *ZF*

Proc. Natl. Acad. Sci. USA (25 April 2016) doi:10.1073/pnas.1515793113

Precursor privileges

Tissue-resident macrophages can be derived from yolk-sac macrophages, fetal-liver monocytes or bone-marrow monocytes. In *Immunity*, van de Laar *et al.* use intranasal transfer of these precursor cells into neonatal *Csf2rb*$^{-/-}$ mice, which have empty alveolar-macrophage niches, to investigate their relative ability to colonize the niche and perform tissue-specific functions. When these progenitors are transferred together in equal ratios, fetal-liver monocytes preferentially (80%) reconstitute the alveolar-macrophage niche in the *Csf2rb*$^{-/-}$ hosts, possibly due to low expression of the receptor for the cytokine GM-CSF on yolk-sac macrophages and poor expression of proliferation-associated genes in bone-marrow monocytes. When transferred separately, all progenitor cells efficiently colonize the niche, acquire an alveolar-macrophage-specific profile with only limited gene-expression differences (7–12 genes) linked to precursor origin, and produce macrophages that are functionally equivalent. In contrast, mature peritoneal, colon and liver macrophages do not colonize this niche after transfer, suggestive of a loss of plasticity in macrophages adapted to other tissues. ***IV***

***Immunity* 44, 755–768 (2016)**

Microbe-activity sensor

Microbial proteases degrade a variety of host proteins. In *Nature Microbiology*, Arase and colleagues show that immunoglobulins cleaved by microbial proteases are detected specifically by the activating receptor LILRA2, which is expressed by myeloid cells. LILRA2 specifically recognizes N-terminally truncated human immunoglobulin M (IgM) and IgG, but not cleaved IgA, and binds to hidden or altered structures in the immunoglobulin light chain exposed by cleavage of the heavy chain. Various microbial pathogens, but not commensal bacteria, cleave human IgM and IgG, and proteases from different microbial pathogens show different immunoglobulin-cleavage patterns. LILRA2-dependent cleaved-immunoglobulin signaling induces IL-8 expression and inhibits the growth of *Legionella pneumophila* in human myeloid cells. Cleaved immunoglobulins are detected in the pus of patients with bacterial infection. The candidate mouse homologs of LILRA, the PIR-A receptors, do not recognize microbially cleaved IgM, and thus the functional mouse homolog of LILRA2 remains unknown. *IV*

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