INFECTION

Iron strength

Cell https://doi.org/10.1016/j.cell.2018.07.016 (2018)

What drives symptomatic or asymptomatic infections remains unclear. In *Cell*, Sanchez et al. investigate the inter-individual, non-genetic variation factors that influence the course of infection. Among mice infected with a 50% lethal dose of the enteric pathogen *Citrobacter rodentium*, healthy infected mice show enrichment for genes involved in iron metabolism in the liver, relative to the expression of such genes in morbid mice, but these mice have similar pathogen loads. Dietary iron protects mice against mortality and gut pathology after infection with doses 1–1,000 times higher than the 100% lethal dose and suppresses the expression of genes involved in *C. rodentium*'s virulence. Dietary iron limits glucose absorption, induces insulin resistance and increases glucose availability in the intestine, which is sufficient for the suppression of virulence-factor-encoding genes, independently of the microbiota. In the long term, dietary iron drives the selection of attenuated strains of *C. rodentium* that establish commensalism. *IV*

https://doi.org/10.1038/s41590-018-0218-8

NK CELLS

TB prognostic marker

Nature https://doi.org/10.1038/s41586-018-0439-x (2018)

The immunological factors that characterize latent tuberculosis infection (LTBI) remain poorly defined. In *Nature*, Chien and colleagues identify stage-specific host responses to infection with *Mycobacterium tuberculosis*. People with LTBI have a higher frequency of $CD16^+$ natural killer (NK) cells and a higher frequency of $GZMB^+PRF^+IFN\text{-}\gamma^+TNF^+$ cells with greater cytotoxic potential among NK cells in the blood than that of uninfected people. Patients with active TB have a lower frequency of NK cells than that of those with LTBI, while successful therapy restores the frequency of NK cells to that in uninfected people. In longitudinal studies, the frequency of NK cells decreases in progressors, remains constant in non-progressors, recovers in those who respond to treatment and remains low in non-responders for a 2-year observation period, indicating that circulating NK cells can be used as an indicator of disease progression. *IV*

https://doi.org/10.1038/s41590-018-0219-7

ANIMAL MODELS

A more human mouse

Nat. Meth. https://doi.org/10.1038/s41592-018-0071-6 (2018)

Humanized mice can address questions not readily amenable to other experimental models, but they lack proper development of secondary lymphoid tissue (SLT) with severely compromised adaptive immunity. In *Nature Methods*, Di Santo and colleagues backcross humanized BALB/c $Rag2^{-/-}Il2rg^{-/-}Sirpa^{NOD}$ mice ('BRGS mice') to mice overexpressing the cytokine TSLP, generating 'BRGST mice'. SLT development is dependent on the function of LTi cells, and the absence of the common γ-chain in BRGS mice means LTi cells fail to develop. However, high TSLP expression in BRGST mice restores LTi cell development and almost completely restores SLT and robust B cell and T cell function. BRGST mice might be a more powerful tool for investigating the human immune system. *ZF*

https://doi.org/10.1038/s41590-018-0220-1

MUCOSAL IMMUNOLOGY

Bleeding anti-inflammatory

Proc. Natl. Acad. Sci. USA https://doi.org/10.1073/pnas.1808426115 (2018)

Hemorrhage releases hemoglobin, which initiates a wound-healing response by macrophages. In the *Proceedings of the National Academy of Sciences*, Takeda and colleagues show that heme induces expression of Spi-C in $CX3CR1^{hi}$ intestinal macrophages. In turn, Spi-C binds to IRF5 and interferes with its ability to drive the expression of select genes encoding pro-inflammatory cytokines, such as *Il1a* and *Il6*. Conditional knockout of Spi-C in macrophages exacerbates experimental colitis, whereas peritoneal delivery of heme ameliorates signs of this disease in a Spi-C-dependent manner. These findings mechanistically link tissue injury in the gut to a macrophage-driven restitutive response. *ZF*

https://doi.org/10.1038/s41590-018-0221-0

IMMUNE EVASION

Viral exploitation of mTOR

Cell **174**, 1143–1157 (2018)

Pox viruses are cytosolic DNA viruses, yet they do not activate cytosolic DNA sensors. In *Cell*, Meade et al. identify a conserved pox virus–encoded protein, F17, that indirectly disrupts sensing by host cGAS and impedes activation of the STING-dependent pathway. F17 competitively binds to Raptor and Rictor and displaces both from mTOR. Rather than impairing mTOR's activity, F17 induces a hyper-activated mTOR state needed for the synthesis of late viral proteins. Concurrently, this dysregulated mTOR localizes to the Golgi, contributing to destabilization of cGAS to suppress the induction of antiviral type I interferon responses. F17 thus mediates viral immune evasion. *LAD*

https://doi.org/10.1038/s41590-018-0223-y

CANCER IMMUNOTHERAPY

Anti-tumor role of metformin

Mol. Cell **71**, 606–620 (2018)

Metformin is prescribed for type 2 diabetes, but anti-tumor effects have also been attributed to metformin. In *Molecular Cell*, Hung and colleagues show that metformin enhances the efficacy of $CD8^+$ T cells by suppressing surface expression of the checkpoint inhibitor PD-L1 on tumor cells. This enhancement of cytotoxicity is dependent on expression of the energy sensor kinase AMPK in tumor cells. Metformin activates AMPK, which in turn phosphorylates newly synthesized PD-L1 within the ER lumen. This phosphorylation of PD-L1 leads to abnormal N-glycosylation of PD-L1 and blocks its maturation within the Golgi, instead triggering ER-associated degradation of PD-L1. Thus, metformin therapy makes tumor cells more vulnerable to cytotoxic T cells. *LAD*

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