Hemozoin powers immunity

An effective vaccine for malaria remains elusive, although there has been some limited success with whole-parasite vaccination. Thus far, most of the research effort on malaria vaccination has focused on parasite antigens; however, a report by Akira and colleagues in *Cell Host and Microbe* looks instead at the adjuvant component of *Plasmodium falciparum* hemozoin, a product of hemoglobin digestion by parasites. Whether hemozoin triggers host Toll-like receptors (TLRs) has until now been controversial. By using knockouts and detailed molecular analysis, the authors definitively demonstrate that hemozoin binds directly to TLR9 in a manner very similar to its better known ligand CpG. It seems that this 'built-in' adjuvanticity of whole-parasite vaccinations might underlie their ability to trigger robust immune responses. The adjuvant properties of synthetic hemozoin are also demonstrated, but this operates in a TLR9-inflammasome–independent way. These findings have important implications for the development of effective malaria vaccines. ***ZF***
***Cell Host Microbe* 1, 50–61 (2010)**

Tickling neutrophils

Although normal gut microflora is thought to exert systemic effects on host immunity, clear evidence for this has been lacking. In *Nature Medicine*, Weiser and colleagues now demonstrate a mechanism by which gut microflora can have far-reaching consequences for the immune system. The gut microbiota is a source of peptidoglycan that translocates from the lumen to the systemic circulation, where it goes on to activate bone marrow–resident neutrophils. Activation in this way is effective in the elimination of pathogenic bacteria such as *Staphylococcus* species. Recognition of peptidoglycan requires expression of the receptor Nod1. Furthermore, germ-free mice show diminished responses to *Staphylococcus*. This study suggests that the systemic immune system is in a persistent state of low activation that is required for rapid pathogen responses. *ZF*
Nat. Med. **16**, 228–231 (2010)

Fat and inflammation

During metabolic diseases, a broad array of inflammatory and stress responses lead to chronic, low-grade local inflammation that further disrupts systemic metabolic homeostasis. In *Cell*, Nakamura *et al.* show that the protein kinase PKR, originally identified as a pathogen sensor that recognizes double-stranded RNA, is also activated by nutrient excess. PKR activation can block insulin action through phosphorylation of IRS1, a critical insulin signaling component. PKR-deficient mice on a high-fat diet have less weight gain, greater glucose tolerance and insulin sensitivity, lower expression of inflammatory mediators and less cell infiltration in fatty tissue than do wild-type mice. The molecular nature of the PKR trigger during nutrient excess remains unknown. Intriguingly, the RNA-binding domain of PKR is indispensable for nutrient-induced activation of PKR. ***IV***
***Cell* 140, 338–348 (2010)**

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

Modulating NF-κB activation

The zinc-finger protein A20 functions as a ubiquitin-editing enzyme to limit the strength and duration of transcription factor NF-κB signaling downstream of the tumor necrosis factor receptor by targeting the adaptor protein RIP1 for degradation by the proteasome. In *Science*, Harjah and colleagues investigate its role in terminating NF-κB signaling downstream of TLRs and show that A20 inhibits the E3 activity of the ubiquitin ligases TRAF6, TRAF2 and cIAP1 by antagonizing their interactions with E2 ubiquitin-conjugating enzymes. A20 binds Ubc13 and UbcH5c in a ZnF4-dependent way and mediates their K48 polyubiquitination and degradation after stimulation with lipopolysaccharide or interleukin 1 and tumor necrosis factor. Interaction between A20 and the regulatory molecule TAX1BP1 is required for these effects. The importance of A20 in limiting inflammation is underscored by the many human autoimmune diseases associated with polymorphisms in the A20 genomic region. *IV*
Science **327**, 1135–139 (2010)

Balancing act

Hypoxia and stress induce the related transcription factors HIF-1α and HIF-2α, but whether these factors have redundant roles is unclear. In *Genes & Development*, Takeda *et al.* show that HIF-1α promotes expression of inducible nitric oxide synthase (iNOS), whereas HIF-2α upregulates arginase I in macrophages. Arginase I and iNOS compete for L-arginine, which is metabolized to nitric oxide by iNOS. Notably, the authors find that both lipopolysaccharide and interferon-γ induce upregulation of HIF-1α and dampen HIF-2α mRNA expression, whereas interleukin 4 enhances HIF-2α expression, albeit with different kinetics. These data are consistent with the M1- and M2-polarization phenotype of macrophages. However, the authors further show that macrophages lacking HIF-2α can express the M2 genes encoding Fizz1 and Ym-1; hence, HIF-2α is not a global M2 regulator. This work does show that HIF-1α and HIF-2α act in an antagonistic way to regulate nitric oxide production and that this effect is influenced by the cytokine environment. ***LAD***
***Genes Dev.* 24, 491–501 (2010)**

Dictating cell fate

Many factors influence effector versus memory T cell fate. In *Immunity*, Shrikant and co-workers show that the energy-sensitive kinase mTOR contributes to this differentiation in naive $CD8^+$ T cells by regulating the transcription factors T-bet and eomesodermin in different ways. Interleukin 12 increases and prolongs mTOR phosphorylation and activity in antigen-activated $CD8^+$ T cells, leading to enhanced interferon-γ expression. Inhibition of mTOR activation with rapamycin does not alter initial interferon-γ expression but blunts cytolytic activity and, unexpectedly, secondary recall responses. Sustained expression of the transcription factor T-bet induced by mTOR is required for T cell effector differentiation. Conversely, rapamycin treatment leads to enhanced eomesodermin expression in wild-type and T-bet-deficient $CD8^+$ T cells, which suggests that mTOR activity regulates the abundance of eomesodermin. Notably, eomesodermin is linked to the generation of T cell memory. More memory T cells are present in mice that receive $CD8^+$ T cells primed in the presence of interleukin 12 and rapamycin than in mice that receive cells primed without rapamycin, although the former can generate robust effector responses after challenge. How mTOR activity is regulated in more physiologic conditions to influence effector versus memory cell fate remains unclear. *LAD*
Immunity **32**, 67–78 (2010)