A quiet place

The bone marrow environment is critical for regulating the quiescence and proliferation of hematopoietic stem cells (HSCs). In *Nature*, Kinisaki *et al.* show that quiescent HSCs associate specifically with small arterioles that are preferentially found in the endosteal bone marrow. Dormant HSCs associate with rare NG2$^+$ periarteriolar pericytes, which are also quiescent and have higher expression of genes associated with 'HSC niche' activity. Depletion of NG2$^+$ cells diminishes the pool of long-term repopulating HSCs in the bone marrow. Pharmacological or genetic activation of the HSC cycle alters the distribution of HSCs from NG2$^+$ periarteriolar niches to LEPR$^+$ perisinusoidal niches. These results indicate that there are spatially distinct, arteriolar and sinusoidal niches for quiescent HSCs versus proliferating HSCs in the bone marrow. ***IV***

Nature **(9 October 2013) doi:10.1038/nature12612**

SNPs for disease prognosis

The clinical course and outcome of disease varies among affected people, but the effect of genetic variability on prognosis is poorly understood. In *Cell*, Lee *et al.* identify a noncoding, T-to-G single-nucleotide polymorphism (SNP) in the gene encoding the transcription factor Foxo3a (*FOXO3A*; SNP rs12212067). Although this SNP does not affect susceptibility to disease, it is associated with milder phenotypes of Crohn's disease and rheumatoid arthritis and a greater risk of severe malaria. The minor *FOXO3A* 'G' allele has a transcription rate up to twofold greater than that of the *FOXO3A* 'T' allele and, consequently, results in faster reaccumulation of FOXO3 in the nucleus. Faster nuclear recovery of FOXO3 initiates a TGF-β-dependent pathway that diminishes the production of proinflammatory cytokines such as TNF, IL-1β and GM-CSF and increases the production of anti-inflammatory IL-10 in monocytes. Polymorphisms in *FOXO3A* have also been associated with human longevity. *IV*

Cell **155**, 57–69 (2013)

DAG sets threshold

Diacylglycerol (DAG) is a second messenger produced downstream of multiple receptors by activation of phospholipase C-γ (PLC-γ). In *Science Signaling*, DeFranco and colleagues show that DAG sets a threshold for the activation of follicular B cells. Expression of diacylglycerol kinase-ζ (DGK-ζ), which terminates DAG-dependent signaling by converting DAG into phosphatidic acid, increases as transitional B cells mature. DGK-ζ regulates the abundance of DAG needed to activate downstream pathways after stimulation of the BCR. Notably, signaling dependent on the kinase Erk is more sensitive to DAG than is signaling via the transcription factor NF-κB. Mice bearing B cells that lack DGK-ζ have more replicating B cells and plasma cells and higher titers of circulating antibody, as the threshold for B cell activation is lower in these mice than in wild-type mice. Thus, DGK-ζ tunes the response of mature B cells by setting a threshold for DAG to activate Erk-dependent pathways. ***LAD***

Sci. Signal. **(15 October 2013) doi:10.1126/scisignal.2004189**

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Thymic B cells

The normal thymus contains a small population of B cells; however, their origin and function has been rather unclear. In the *Proceedings of the National Academy of Sciences,* Huang and colleagues observe that those B cells develop from progenitors in the thymus with minimal contribution from the peripheral B cell pool. The thymic B cell population is phenotypically distinct from both follicular B cells and B-1 cells. Thymic B cells also have high expression of major histocompatibility complex class II and costimulatory molecules and are adept at antigen presentation. Thymic B cells are present at the cortico-medullary junction, which suggests that they may be involved in the negative selection of T cells. Indeed, through the use of a system with transgenic expression of BCRs and TCRs, the authors find that autoreactive B cells can contribute to the negative selection of T cells. Therefore, thymic B cells may be involved in 'pruning' certain subsets of autoreactive T cells. *ZF*

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Help for helminths

The helminth *Schistosoma mansoni* cannot develop productively in hosts deficient in recombination-activating gene 1 (*Rag1*$^{-/-}$ hosts); this suggests that an intact host immune system is necessary for parasite growth, but the precise nature of the signals required remains unclear. In *PLoS Pathogens*, Davies and colleagues find that infection with *S. mansoni* results in hepatocyte necrosis in wild-type mice but not in *Rag1*$^{-/-}$ mice. Recapitulating that injury in *Rag1*$^{-/-}$ mice with hepatotoxic drugs or via challenge with endogenous damage-associated molecular patterns can partially restore parasite development. Such treatment results in the release of inflammatory cytokines, which is reined in by innate tolerance mechanisms after a few weeks. That tolerance is critical for the parasite because if the inflammation is maintained chronically, their growth is completely repressed. Administration of IL-4 is also able to restore parasite growth in *Rag1*$^{-/-}$ mice, again through the antagonism of inflammatory responses. Therefore, the developmental fate of *S. mansoni* seems to be intimately entwined with the prevailing host immune response. ***ZF***

PLoS Pathog. **(10 October 2013) doi:10.1371/journal.ppat.1003708**

Zinc deprivation

Macrophages contribute to the control of microbial infection by phagocytosis of extracellular bacteria and fungi; however, some pathogenic microbes can survive in phagosomes. In *Immunity*, Vignesh *et al.* demonstrate how macrophages kill engulfed pathogenic fungi by limiting the availability of zinc in phagosomes. Macrophages stimulated with the cytokine GM-CSF upregulate expression of zinc-chelating metallothioneins and the zinc transporters Slc39a2, Slc30a4 and Slc30a7. Although activated macrophages import more zinc, the net effect is that zinc is removed from phagocytic vesicles and accumulates in the Golgi, thus depriving engulfed microbes from available zinc. GM-CSF-induced sequestration of zinc also increases the oxidative burst mediated by NAPDH oxidase in infected macrophages. Thus, GM-CSF enhances macrophage-mediated microbial killing by regulating zinc accessibility. *LAD*

Immunity **39**, 697–710 (2013)