The survival factor

Neutrophils, eosinophils and Ly6C^{hi} monocytes have a short lifespan. In *Nature*, Hernao-Mejia and colleagues show that these immune cells have high expression of the long noncoding RNA *Morrbid* and that it controls their survival. *Morrbid*-deficient mice have specific loss of eosinophils, neutrophils, Ly6C^{hi} and Ly6C^{lo} monocytes but not of other immune cells. The effect is cell intrinsic and is restricted to mature cells. *Morrbid*-deficient short-lived myeloid cells have greater apoptosis and higher expression of the gene encoding the pro-apoptotic molecule Bim. The cytokines IL-3, IL-5 and GM-CSF, which promote the survival of short-lived myeloid cells, induce *Morrbid* expression. *Morrbid* represses *Bim* through direct interaction with the Ezh2 subunit of the repressive complex PRC2 and recruitment of PRC2 to the *Bim* promoter through DNA looping in *cis* between the *Morrbid* and *Bim* loci. Inhibition of PCR2 induces apoptosis in wild-type eosinophils but not in Bim-deficient eosinophils. ***IV***

Nature **(15 August 2016) doi:10.1038/nature19346**

Shaping the healthy repertoire

Although much is known about the generation and maintenance of memory T cells after infection, less is known about the fate and repertoire of such cells that arise naturally through life under homeostatic conditions. In the *Proceedings of the National Academy of Sciences*, Zhuang and colleagues use a novel fate-tracing system that allows T cells to be tracked over long time spans. As expected, mice 1.5 years of age have diminished thymic output but also have long-lived clones with greater representation of regulatory T cells than of conventional T cells. Repertoire analysis shows that the long-lived populations of conventional T cells and regulatory T cells share overlapping clonotypes that are consistent among different mice in similar housing conditions. The unambiguous enrichment for restricted regulatory T cell clonotypes suggests that they are being selected throughout the life of the host to maintain tolerance to self antigens and commensals. *ZF*

Proc. Natl. Acad. Sci. USA (17 August 2016) doi:10.1073/pnas.1601634113

Fueling IgA production

Intestinal microbiota and their metabolites can regulate both local and systemic immunity. In *Cell Host and Microbe*, Kim and colleagues find that short-chain fatty acids (SCFAs) produced by bacterial fermentation of dietary fiber modulate the production of immunoglobulin A (IgA) in the gut. Mice fed low-fiber diets generate fewer IgA$^+$ B cells and IgA-producing plasma cells in a microbiota-dependent manner. Administration of SCFAs themselves produces a similar effect through an increase in IgA production and directly skews the B cell transcriptional program toward antibody production, probably through the deacetylase-inhibitory activity of SCFAs. Another important function of the SCFAs is their help in driving the metabolically demanding activity of class switching and antibody synthesis by boosting B cell glycolysis. A diet rich in fiber and SCFAs helps to support an effective IgA-mediated response to the gut pathogen *Citrobacter rodentium*. ***ZF***

Cell Host Microbe **20, 202–214 (2016)**

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

Macrophage core program

The mechanisms that control the diversification of tissue-resident macrophages remain unclear. In *Science*, Geissmann and colleagues perform spatio-temporal analysis of macrophage development in mice. Transcriptional profiling of embryonic erythro-myeloid progenitors, fetal CD45$^+$Lin$^-$c-kit$^-$ pre-macrophages and F4/80$^+$ adult tissue macrophages identifies a core macrophage transcriptional program, including expression of the transcription-factor-encoding genes *Csf1r*, *Maf*, *Batf3*, *Pparg*, *Irf8* and *Zeb2*, that is acquired in pre-macrophages as they colonize the embryo in a manner dependent on the chemokine receptor CX3CR1. Tissue-specific signatures are acquired in each population as early as embryonic day 12.5 in microglia, Kupffer cells and kidney macrophages or undergo postnatal changes in Langerhans cells and alveolar macrophages. Genes encoding some tissue-specific factors are expressed as early as embryonic day 10.26 in tissue macrophages (*Sall1* and *Sall3*) or are expressed in erythro-myeloid progenitors or pre-macrophages (*Id1* and *Sall3*) before their expression becomes restricted to a certain macrophage subset. The transcription factor Id3 emerges as being important for the development and maintenance of Kupffer cells. *IV*

Science (4 August 2016) doi:10.1126/science.aaf4238

Neutrophilic tumor suppressors

Myeloid suppressor cells are commonly found in tumors and contribute to the immunosuppressive microenvironment. In *Science Immunology*, Condamine *et al.* identify a population of suppressive polymorphonuclear cells present in the circulation and within tumors obtained from patients with cancer. These human suppressor cells express the lectin-type oxidized low-density lipoprotein receptor LOX-1 and exhibit differences in gene expression that distinguish them from normal neutrophils obtained from the same patients and healthy donors. This distinct gene profile is associated with the induction of endoplasmic reticulum stress and expression of the transcription factor sXBP-1. Treatment of normal neutrophils with thapsigargin leads to their acquisition of immunosuppressive activity, whereas inhibitors of XBP-1 prevent such activity. These findings provide a new tumor biomarker, LOX-1, and suggest a means by which such cells might be targeted for therapeutic benefit. ***LAD***

Sci. Immunol. **1, aaf8943 (2016)**

Germline TCR contributions

Highly diverse repertoires of T cell antigen receptors (TCRs) arise from somatic combinatorial rearrangement of variable-diversity-joining gene segments encoding TCR chains. It remains controversial, however, whether germline-encoded variants can select for particular TCR–major histocompatibility complex (MHC) interactions. In *Nature Genetics*, Sharon *et al.* utilize expression-quantitative-trait-locus mapping to analyze the expression of TCR-encoding genes in a large human cohort of European ancestry. They identify multiple highly significant MHC-TCR genetic associations indicative of selective pressure for distinct contact interactions. These contacts are especially significant for variable-region-encoded complementarity-determining regions CDR1 and CDR2 of the TCRα chains that interact with HLA-B chains. These findings support the hypothesis that germline contributions influence the recognition of MHC molecules by TCRs and the selection of expressed TCR repertoires, which results in distinct combinations of TCR-MHC interactions. *LAD*

Nat. Genet. (1 August 2016) doi:10.1038/ng.3625