TRANSCRIPTIONAL REGULATION

Both local and global

Cell https://doi.org/10.1016/j.cell.2018.04.018 (2018)

How pioneer transcription factors (TFs) bind in a cell type–specific manner has remained unclear. In *Cell*, Glass and colleagues evaluate the effect of single-nucleotide polymorphisms and of insertions or deletions on TF binding and gene expression in bone marrow–derived macrophages from five inbred mouse strains. They find that expression of 10% of all transcripts varies by at least fourfold across the five strains. TF binding is affected more by genetic variation than by active histone modifications, nascent RNA production or mature RNA transcripts. Strain-specific differences result mainly from variation in distal cis-regulatory elements. The majority of strain-specific TF binding correlates with variation in binding sites for a network of TFs located nearby, but some is due to regional interactions between cis-regulatory elements, independently of local genetic variation. *IV*

https://doi.org/10.1038/s41590-018-0146-7

MICROBIOTA

Fiber against flu

Immunity **48**, 992–1005 (2018)

Dietary fiber provides protection against chronic and allergic airway inflammation. In *Immunity*, Marsland and colleagues show that a high-fiber diet (HFiD) also ameliorates the lung pathology of influenza virus–infected mice. Mice fed the HFiD, which increases the production of short-chain fatty acids by the intestinal microbiota, or mice given direct supplementation with the short-chain fatty acid butyrate, have greater differentiation of Ly6C$^-$ monocytes and tissue repair–prone interstitial and alveolar macrophages, less production of the neutrophil chemoattractant CXCL1, and less infiltration of neutrophils in the lungs than that of mice fed a low-fiber diet. In addition, the HFiD and butyrate directly enhance the metabolism of CD8$^+$ T cells, which results in greater population expansion of virus-specific cells and enhanced cytotoxic capacity. The effects are mediated through the G protein–coupled receptor GPR41. *IV*

https://doi.org/10.1038/s41590-018-0147-6

RATIONAL VACCINE DESIGN

Targeting Ebola

Nat. Microbiol. **3**, 670–677 (2018)

Developing an effective vaccine against Ebola virus and other related filoviruses is a top priority for global health organizations. In *Nature Microbiology*, Flyak et al. provide insights into rational vaccine design steered by the characterization of broadly neutralizing antibodies derived from patients who survived infection with Bundibugyo virus, a member of the genus *Ebolavirus*. Three cross-neutralizing monoclonal antibodies recognize a conserved epitope, HR2-MPER, that is present near the membrane-proximal external region of viral glycoproteins. This epitope is distinct from previously identified Ebola virus–specific glycoprotein epitopes. Animal-vaccination models show that HR2-MPER peptides can elicit neutralizing antibodies and confer protection against subsequent challenge with Ebola virus. This discovery should aid in the design of vaccines against Ebola virus and emerging filoviral pathogens. *LAD*

https://doi.org/10.1038/s41590-018-0148-5

TUMOR IMMUNOLOGY

TILs on standby

Nature https://doi.org/10.1038/s41586-018-0130-2 (2018)

The immunological-checkpoint therapy used for cancer operates mainly by unleashing the effector function of cytotoxic T lymphocytes. In *Nature*, Newell and colleagues examine human colon and lung tumors and find that tumor-infiltrating lymphocytes (TILs) are very heterogeneous. Not only are there TILs specific for the tumor, as expected, but also there are large numbers of TILs present that are not specific for tumor antigens, and some of these bystander TILs are even specific for viral antigens. These two categories of TILs have distinct phenotypes: the tumor-specific TILs express the ATP ectonucleotidase CD39 and have a chronically activated and exhausted signature, whereas the bystander TILs lack CD39 and signs of exhaustion. CD39 might therefore serve as a useful biomarker for the isolation of tumor-specific cytotoxic T lymphocytes. *ZF*

https://doi.org/10.1038/s41590-018-0150-y

CANCER IMMUNOTHERAPY

4PD1^{hi} T cells

Cancer Cell **33**, 1017–1032 (2018)

Cancer clinical trials are underway to target the immunological co-inhibitory receptors PD-1 or CTLA-4; however, such checkpoint therapies are effective in only a fraction of patients. In *Cancer Cell*, Zappasodi et al. identify a population of suppressor CD4$^+$Foxp3$^-$ T cells, called '4PD1^{hi} T cells', that accumulate within tumors and are poor prognostic indicators. 4PD1^{hi} T cells are able to inhibit both CD4$^+$ effector cells and CD8$^+$ effector cells. RNA-based sequencing expression profiles show that 4PD1^{hi} T cells are distinct from Foxp3$^+$ regulatory T cells; instead, these cells resemble CD4$^+$ follicular helper T cells. In melanoma models and in patients, mono-therapy with antibody to PD-1 diminishes the frequency of 4PD1^{hi} T cells, whereas antibody to CTLA-4 increases their frequency, which suggests that clinical monitoring of 4PD1^{hi} T cells is warranted for treatment decisions. *LAD*

https://doi.org/10.1038/s41590-018-0149-4

VACCINATION

Dysbiosis shapes vaccine responses

Cell Host Microbe https://doi.org/10.1016/j.chom.2018.04.009 (2018)

Vaccine responses can vary considerably among people, with both genetic factors and environmental factors exerting an influence. In *Cell Host and Microbe*, Lynn and colleagues use a mouse model to assess the effect of early-life exposure to antibiotics (ampicillin and neomycin) on responses to five different vaccines. In all cases, early exposure to antibiotics results in impaired antibody responses. In contrast, T cell cytokine responses are intact or even enhanced. Exposure of adult mice to antibiotics does not impair vaccine responses. The impairment of antibody responses seems to be dependent on antibiotic-driven dysbiosis rather than on direct effects of the antibiotics themselves. Understanding the microbiotal factors that shape vaccine responses might help in the tailoring of vaccinations, such as by the inclusion of probiotics. *ZF*

https://doi.org/10.1038/s41590-018-0151-x

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