CANCER IMMUNOTHERAPY

## Targeting TGF-β in cancer

*Nature* **554**, 538–543 & 544–548 (2018)

Increased expression of the morphogen TGF-β is associated with poor prognosis in many cancers. In *Nature*, Tauriello et al. and Mariathasan et al. show that more TGF-β in the tumor environment is a chief mechanism for evading the immune system and that blockade of TGF-β acts in synergy with PD-L1 checkpoint blockade to induce tumor regression. In a mouse model of colorectal cancer, Tauriello et al. show that cancer-associated fibroblasts are the main contributors to TGF-β production and that a TGF-β inhibitor induces the enhanced infiltration of cytotoxic T cells and the $T_H1$ subset of helper T cells into primary tumors and liver metastases. Mariathasan et al. show that in patients with metastatic urothelial cancer, a TGF-β-response signature in cancer-associated fibroblasts is associated with non-responsiveness to PD-L1 blockade in excluded tumors only, whereas tumor-mutational burden correlates with responsiveness in inflamed tumors only. *IV*

https://doi.org/10.1038/s41590-018-0076-4

AUTOIMMUNITY SUSCEPTIBILITY

## Mast cells in autoimmune disease

*Proc. Natl. Acad. Sci. USA*
https://doi.org/10.1073/pnas.1710401115 (2018)

There is a well-known skewing in the incidence and severity of multiple sclerosis in human females, a relationship that is reflected in at least some strains of mice. In *The Proceedings of the National Academy of Sciences USA*, Brown and colleagues use an SJL mouse model of experimental autoimmune encephalitis to explore the mechanistic basis of this sex difference in disease susceptibility. After immunization with myelin peptide, female mice have a greater abundance of encephalitogenic cells of the $T_H17$ subset of helper T cells, whereas male mice show a more protective type 2–shifted immunity. Mechanistically, testosterone acts on mast cells, which in turn produce the cytokine IL-33 that drives the activation of type 2 innate lymphoid cells. The absolute amount of testosterone is not the only factor in play; instead, male mouse–derived mast cells show an intrinsically greater proclivity to produce IL-33. *ZF*

https://doi.org/10.1038/s41590-018-0080-8

EPIGENETICS

## Establishing T cell lineage identity

*Immunity* **48**, 243–257 (2018)

Lineage-determining transcription factors regulate chromatin accessibility and transcriptional output. In *Immunity*, Vahedi and colleagues show that the transcription factor TCF-1 controls T cell fate by targeting silent chromatin and inducing chromatin accessibility at T cell–specific loci. The authors observe three waves of chromatin remodeling during T cell development: at the ETP stage, the DN2b stage and the SP stage. TCF-1 shows the greatest enrichment for recognition sites and the most binding in regulatory regions that become accessible during the ETP and DN2b wave and persist until maturation, in both humans and mice. Chromatin accessibility is lost in these loci in TCF-1-deficient $CD4^+CD8^+$ double-positive thymocytes. Ectopic expression of TCF-1 induces de novo chromatin accessibility and expression of T cell–specific genes such as *Bcl11b*, *Il2rb, Ccr7* and *Icosl* in non-hematopoietic cells such as fibroblasts. *IV*

https://doi.org/10.1038/s41590-018-0077-3

UNEQUAL CELL DIVISION

## Asymmetry in PI(3)K activity

*Cell Rep.* **22**, 860–868 (2018)

Unequal cell division leads to distinct daughter-cell fates. In *Cell Reports*, Reiner and colleagues report that activated lymphocytes show polarization of phosphatidylinositol-(3,4,5)-triphosphate and phosphatidylinositol-3-OH kinase (PI(3)K), initiated during the formation of immune synapses, that is aligned with microtubule-organizing centers and is maintained throughout cell division. This asymmetry of PI(3)K activity also causes unequal division of nutrient receptors, such as the glucose transporter Glut1, between sibling daughter cells during cytokinesis and thereby establishes differences in their metabolic capacity. T cells with higher expression of Glut1 suppress expression of the transcription factor TCF-1; similarly, B cells with high expression of Glut1 downregulate expression of the transcription factor Pax5. These findings suggest that cellular asymmetry in PI(3)K can lead to differences in cell-fate potential. *LAD*

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NEUROIMMUNOLOGY

## Neuroregulation of ILC2s

*Science* **359**, 1056–1061 (2018)

Group 2 innate lymphoid cells (ILC2s) protect mucosal barriers against helminths, allergens and other noxious stimuli. In *Science*, Moriyama et al. reveal a negative regulatory interaction between adrenergic neurons and ILC2s that reside in close proximity in the gut and lungs. Human and mouse ILC2s express $\beta_2$-adrenergic receptors ($\beta_2$-ARs) that respond to norepinephrine and other $\beta_2$-AR agonists. Mice that lack $\beta_2$-AR expression have a frequency of ILC2s similar to that of wild-type mice at steady state but exhibit enhanced eosinophilia, mucus production and worm expulsion after helminth infection. Agonist stimulation of $\beta_2$-AR signaling suppresses the infection-induced proliferation of ILC2s and thereby diminishes type 2 immune responses. Thus, adrenergic neuron–ILC2 interactions are tuned to avoid over-exuberant type 2 inflammatory responses. *LAD*

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FLOW CYTOMETRY

## Flowing into higher dimensions

*Cytometry A*. https://doi.org/10.1002/cyto.a.23331 (2018)

High-dimensional analysis of immune cells is becoming increasingly prevalent in immunology and can provide in-depth information on rare or transitional populations; however, it can be technically challenging and expensive and can require the use of highly specialized reagents. In *Cytometry A*, Mair and Prlic describe a conventional flow-cytometry staining panel that incorporates 28 colors plus two physical parameters (forward scatter and side scatter). The panel covers all canonical human dendritic-cell subsets but also allows parallel analysis of monocytes and lymphocytes. The 30 parameters presented enable the description of human cells by flow cytometry in unparalleled depth without the need for 'bespoke' equipment or reagents and approach the dimensionality of more-specialized technologies such as mass cytometry. *ZF*

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