NEUROIMMUNOLOGY

Modeling AD

Nat. Neurosci. https://doi.org/10.1038/s41593-018-0175-4 (2018)

The pathogenesis of Alzheimer's disease (AD) is poorly understood, in part due to the lack of models that recapitulate the disease. In *Nature Neuroscience*, Cho and colleagues describe a human cell-culture model of neurons, astrocytes and microglia in a three-dimensional microfluidic platform. Neuron and astrocyte cultures derived from human neural progenitor cells transduced with human Aβ precursor protein containing substitutions associated with familial AD reproduce characteristics of AD, such as aggregation of Aβ, production of inflammatory mediators (CCL2, TNF and IFN-γ) and accumulation of phosphorylated tau protein, and induce the activation and recruitment of microglia seeded in distal chambers. The recruited microglia induce the loss of neurons and astrocytes, retraction of neurites and production of mediators of inflammation in a manner dependent on the receptor TLR4. Thus, the model reproduces physiologically relevant interactions in AD. *IV*

https://doi.org/10.1038/s41590-018-0171-6

NEUROIMMUNOLOGY

Triggering myelopoiesis

Immunity https://doi.org/10.1016/j.immuni.2018.05.004 (2018)

Diabetes is often accompanied by hypertension, augmented activation of the sympathetic nervous system (SNS) and inflammation. In *Immunity*, Dutta and colleagues identify a link between SNS signaling and increased splenic myelopoiesis. Diabetic mice show enhanced splenic myelopoiesis; this results from greater SNS activity and production of catecholamines, which act on granulocyte-macrophage progenitors. Sympathetic nerves signal via neuropeptides to tyrosine hydroxylase–expressing leukocytes. Granulocyte-macrophage progenitors proliferate and differentiate in response to SNS signals, whereas ablation of tyrosine hydroxylase–positive cells, blockade of β_2-adrenergic receptors or splenic sympathectomy normalizes the number of myeloid cells in diabetic mice. These findings reveal that neuroimmunological signaling within the spleen results in increased 'emergency' myelopoiesis. *LAD*

https://doi.org/10.1038/s41590-018-0172-5

ADOPTIVE IMMUNOTHERAPY

TILs show the way

Nat. Med. https://doi.org/10.1038/s41591-018-0040-8 (2018)

In *Nature Medicine*, Feldman and colleagues use a highly personalized adoptive-therapy approach to successfully treat a patient with metastatic ER^+HER2^- breast cancer that was refractory to chemotherapy. Whole-exome sequencing of the tumor revealed extensive non-synonymous mutations. After population expansion of tumor-infiltrating lymphocytes (TILs) ex vivo, over 80 billion TILs were re-infused to the patient, in tandem with the cytokine IL-2 and pembrolizumab (antibody to the co-inhibitory molecule PD-1). A total of eleven clonotypes recognized four different tumor neoantigens, most of which persisted long term in the patient (at least 17 months). Resolution of all tumor lesions was seen at 1 year after TIL infusion, and the patient remained clear >22 months later. This demonstrates the beneficial results that can be achieved with a highly personalized TIL adoptive-transfer approach. *ZF*

https://doi.org/10.1038/s41590-018-0175-2

MICROBIOTA

Symbionts and metabolites

Cell https://doi.org/10.1016/j.cell.2018.05.014 (2018)

Intestinal parasites such as helminths or the protozoan *Tritrichomonas* induce the accumulation of tuft cells and goblet cells in the small intestine of mice through induction of the cytokine IL-13 in group 2 innate lymphoid cells (ILC2s). In *Cell*, Locksley and colleagues show that tuft cells are very rare in the first 2 weeks of life and accumulate after weaning through a process that is dependent on IL-25 and is negatively regulated by the ubiquitin-editing protein A20, which restricts signaling through the IL-25 receptor in ILC2s. Tuft-cell accumulation depends on colonization with *Tritrichomonas*, dietary fibers and succinate, which can directly induce IL-25 production in tuft cells, and is independent of bacterial microbiota, acetate, butyrate and propionate. Colonization with *Tritrichomonas* or treatment with IL-25 increases the resistance of mice to infection to *Nippostrongylus brasiliensis* or *Heligmosomoides polygyrus*. *IV*

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TUMOR IMMUNOLOGY

Autophagy & MDSCs

J. Clin. Invest. https://doi.org/10.1172/JCI120888 (2018)

Myeloid-derived suppressor cells (MDSCs) within tumors block the anti-tumor action of immune effector cells. In *The Journal of Clinical Investigation*, Alissafi et al. show that MDSCs rely on autophagy–lysosomal pathways to promote immunosuppression. Tumor growth is diminished in mice with myeloid cell–specific deletion of *Atg5*, which encodes a key component of autophagy. ATG5-deficient myeloid cells still accumulate in tumors but promote anti-tumor responses by their increased expression of major histocompatibility complex class II and co-stimulatory molecules and decreased suppressor activity. Interfering with the fusion of autophagosomes with lysosomes or lysosomal function also impairs the suppressor activity of MDSCs. Thus, interfering with the autophagy program represents an 'Achilles' heel' through which to target MDSCs to enhance anti-tumor immune responses. *LAD*

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NANOPARTICLES

A harmful pairing

Proc. Natl Acad. Sci. USA https://doi.org/10.1073/pnas.1804542115 (2018)

Environmental nanoparticles, such as those derived from industrial processes or diesel fumes, can exacerbate inflammatory responses. In the *Proceedings of the National Academy of Sciences USA*, Stauber and colleagues demonstrate that fungal spores collected under real-world conditions are frequently coated with nanoparticles such as silica. Nanoparticles adsorb onto spores rapidly and stably and shield them from destruction by antimicrobial defensins and impair phagocytosis, yet nanoparticle-coated spores trigger greater production of inflammatory cytokines by macrophages and neutrophils. Nanoparticle-decorated *Aspergillus fumigatus* spores are also more harmful when instilled into mouse lungs. These results suggest that not only can nanoparticles directly damage lung epithelium but they can also act in synergy with the pathobiology of *A. fumigatus*. *ZF*

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