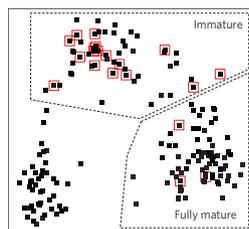


NEUROBIOLOGY

Tracking the scent

Science 350, 1251-1255 (2015);
Mol. Syst. Biol. 11, 844 (2015)

MOL. SYST. BIOL.



Olfactory sensory neurons are believed to follow a ‘one-neuron-one-receptor’ rule to properly translate odor signals into the brain. However, the complexity of the olfactory system—which displays continuous neurogenesis, with more than 1,000 olfactory receptor genes expressed in several developmental stages—has limited detailed analyses. Two studies now report the application of single-cell transcriptomics of mouse olfactory epithelium to investigate this system. Hanchate *et al.* and Tan *et al.* first used genetic markers to assign cells to different developmental stages. Separately, they examined olfactory receptor expression, with Hanchate *et al.* finding that this began to appear in precursor neurons and was well established in the immature neurons. Tan *et al.* noted that some cells expressed multiple splicing isoforms of the same receptors, and identified new isoforms. Furthermore, both studies reported coexpression of multiple distinct olfactory receptors in a subset of cells, primarily immature neurons. Initial analysis of tissue sections confirmed that

these observations were not an artifact of cell handling. Finally, Hanchate *et al.* determined that olfactory receptor expression does seem to be linked to the identity of receptors expressed in the same nasal zone, but not to receptor-induced neuronal activity. Tan *et al.* extended the conclusion to a related gene family that senses volatile amines. Further work will be needed to determine which of several proposed mechanisms leads to the ‘one-neuron-one-receptor’ phenotype. CG

ANTIVIRALS

Alphaviruses feel the STING

PLoS Pathog. doi:10.1371/journal.ppat.1005324

Given the role of innate immune processes in inhibiting viral infection, pharmacologic activation of innate immunity represents an attractive antiviral strategy. Innate signaling cascades often culminate with the synthesis of type I interferons (IFNs) after initial recognition of microbe-associated molecules by pattern-recognition receptors (PRRs). To identify compounds that can stimulate IFN production as leads for new antivirals, Sali *et al.* performed a high-throughput screen for compounds that could activate a reporter under the control of an IFN- and IRF3-dependent promoter. IRF3 is a transcription factor required for PRR-mediated IFN β transcription. The authors focused on one compound, G10, and found that it exhibits antiviral activity against the human pathogens Chikungunya and Venezuelan equine encephalitis viruses, two emerging mosquito-transmitted alphaviruses. Using a CRISPR-Cas9-mediated gene knockout approach, they found that G10’s antiviral activity required IRF3 activation as well as

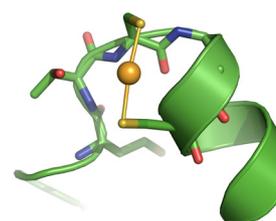
STING, a PRR for cyclic dinucleotides. The authors could not observe direct binding of G10 to STING, and no target protein was immediately identified; instead, the authors hypothesize that another upstream PRR acts as the efficacy target of G10. These results suggest that pharmacologic targeting of STING-dependent, IRF3-terminal signaling pathways represents a potentially viable antiviral strategy. MB

METALLOENZYMES

Getting the gold

J. Am. Chem. Soc. 137, 15358-15361 (2015)

J. AM. CHEM. SOC.



Gold-thiol bonds form the basis of many nanotechnology and materials platforms, with existing characterization suggesting that the strengths of the bonds vary widely depending on local conditions. Wei *et al.* now use single-molecule force spectroscopy and X-ray crystallography to examine these interactions in the context of a recently discovered gold-binding protein, GolB. For the force spectroscopy studies, the authors created a chimera containing four repeats of GolB coupled with a fast-folding β -hairpin reporter. When GolB was in the apo form, the forces needed to unfold it were below the instrumental detection limit. Upon addition of gold ions, peaks were observed corresponding to forces of 165 ± 55 pN, much lower than seen in non-biological contexts but similar to results from previous studies on the strengths of proteinaceous iron-sulfur bonds. Though GolB is functionally able to discriminate gold from copper, the forces needed to unfold Cu-loaded GolB were similar to those for Au-loaded species, suggesting that GolB’s specificity is not linked to the strength of binding. The long S-Au bonds observed in the GolB crystal structure, in which the chelation strength of the thiolates is likely attenuated by neighboring groups, provide a rationale for the low mechanical strength. The authors hypothesize that these weak bonds are what enable GolB to serve as a gold-specific chaperone. CG

Written by Mirella Bucci, Catherine Goodman & Stéphane Larochelle

OXIDATIVE DAMAGE

A pathway to stress

Nat. Commun. 6, 10112 (2015)

Chemotherapy is known to trigger oxidative DNA damage and reactive oxygen species (ROS)-mediated cell death, which can cause harmful side effects. Because leukotriene C₄ (LCT₄)—a signaling molecule best known for being secreted by mast cells during allergic reactions—had previously been shown to trigger cellular ROS accumulation, Dvash *et al.* decided to investigate the potential role of LCT₄ production in the oxidative stress response in non-hematopoietic cells. The authors’ initial observation was that enzymes involved in leukotriene biosynthesis, including glutathione S-transferase 2 (MGST2), are upregulated and accumulate in the nucleus in response to endoplasmic reticulum (ER) stress, triggering LCT₄ production. This synthetic pathway is distinct from that found in hematopoietic cell lineages, which uniquely express LCT₄ synthase, an MGST2 isozyme. The authors then demonstrated that LCT₄ accumulation mediates chemotherapeutic agent-triggered oxidative damage and that the cytotoxicity of those treatments can be greatly reduced in mouse models by interfering with the production or action of LCT₄—either through *Mgst2* deficiency or through the application of LCT₄ antagonists commonly used in asthma treatment. In addition to uncovering a novel pathway to LCT₄ biosynthesis in non-hematopoietic cells triggered by ER stress, the work suggests potential clinical applications for LCT₄ antagonists in mediating the side effects of cytotoxic chemotherapy. SL