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SPRINGER NATURE

BIOLOGICAL MODELS

A fish for melanoma's origins

Dis. Model Mech. doi:10.1242/dmm.030056 (2018)

Before a cancer can progress to a solid tumor, the first cancerous cells must evade the immune system. Immune cells normally involved in inflammatory responses can be co-opted by malignant melanocytes, but the exact signaling pathways involved are unclear, and it has been difficult to predict when and where the initial immunosuppression occurs that allows the cancer to proliferate. To help investigate the early origins of melanoma, researchers at Oxford present a new inducible zebrafish model.

Their transgenic fish contains oncogenes that can be activated specifically in melanocytes with a synthetic hormone called mifepristone, allowing temporal control. A new biotinylation method allows them to tag and then isolate specific immune cells in specific tissues for transcriptomic analysis. With the new line, they were able to follow immune responses from the very beginning of oncogene activation. *EPN*

<https://doi.org/10.1038/s41684-018-0054-3>

BIOLOGICAL MODELS

CRISPR through to emphysema

PNAS **115**, 2788–2793 (2018)

Humans have a single gene that codes the alpha-1 antitrypsin protein; mutations that cause deficiencies can contribute to pulmonary diseases like emphysema. Mice have six, complicating efforts in the past to create genetic animal models. But those extra genes have proved no match for CRISPR.

Using the gene-editing technology to target conserved regions across the murine genes, researchers led by Chris Mueller at the University of Massachusetts Medical School managed to knock out five of those paralogs. Symptoms characteristic of emphysema can be induced in young mice with a lipopolysaccharide challenge, but will also spontaneously develop as the mice age. *EPN*

<https://doi.org/10.1038/s41684-018-0055-2>

IMMUNOLOGY

A wild outcome

PLoS Biol. **16**, e2004108 (2018).

What controls a phenotype? In the lab, the environment is tightly controlled to help tease out the relationship between

an organism's underlying genotype and a resulting phenotype. But the larger world is not so uniform, and environmental differences can cause drastically different outcomes. Andrea Graham, a researcher at Princeton University interested in better understanding the immune system, is investigating that by letting lab mice go 'wild' at a farm in New Jersey.

In her lab's latest paper, they compare nematode infections in conventionally clean C57BL/6 mice and in the same strain living outdoors. Indoor mice easily fought off the parasites, but wild mice didn't; the longer they were outside, the more worms they carried. Their gut microbes changed on the farm, as did their immune responses. Nature—the environmental kind—is an important consideration. *EPN*

<https://doi.org/10.1038/s41684-018-0056-1>

VIRUSES

Size matters for the flu

PNAS **115**, E2386–E2392 (2018)

Influenza can be spread by contact, droplets that are coughed or sneezed out and land on a mucus membrane, or airborne transmission of dried particles that are later inhaled. Little is known about the relative contribution of each mode to the overall spread of flu. A team of Chinese and US researchers designed a transmission chamber that can trap and remove particles by size and used it to determine the particle sizes responsible for transmitting human influenza virus from one ferret to another.

Spread of flu was driven by large particles (>1.5 µm), however there was some difference between different virus strains. A more complete understanding of how different particle sizes contribute to infections could improve prevention efforts. The researchers' chamber could also be applied to other animal models of disease transmission. *JK*

<https://doi.org/10.1038/s41684-018-0057-0>

METABOLISM

Where's the sweet stuff?

Cell Metab. **27**, 351–361 (2018)

Glucose and fructose have the same six-carbon molecular structure but may differ in how they affect the body, with high consumption of fructose a suspected contributor to metabolic disease. Differences in how the sugars are metabolized are under investigation, but just where that metabolism is happening may have been an overlooked detail.

Previously, the liver was considered the primary site of sugar metabolism. But with the help of isotope tracers, a new study in C56BL/6 mice shows that, at low dietary doses, fructose doesn't reach the liver; instead, it's converted to glucose and other related metabolites in the small intestines. But as doses increase, the intestines can't keep up, leaving the liver, as well as bacteria in the colon, to handle the excess fructose. *EPN*

<https://doi.org/10.1038/s41684-018-0058-z>

PHENOTYPES

Not so simple

PLoS Genet. **13**, e1007075 (2017)

A particular mutation in a given gene doesn't always result in the same phenotype. Genes interact with each other as well as with the environment; without proper understanding of what those interactions are, assigning particular functions and predicting results can be fraught. A new study systematically analyzes how genetic background and the environment influence expression and complementation of alleles of the *scalloped* and *vestigial* genes that give shape to *Drosophila* wings. Different mutations were introduced to different genetic backgrounds, and flies were also reared at different temperatures. The results indicate that context matters: an array of different wing shapes were produced that varied with the different combinations tested, some more strongly than others. *EPN*

<https://doi.org/10.1038/s41684-018-0061-4>

SPINAL CORD INJURY

Mind around the gap

Nat Neurosci. **21**, 576–588 (2018)

In rodents, models of spinal cord injury (SCI) that involve carefully cutting the spine have revealed important pathways and improved understanding of how neurons can repair themselves post-injury. However, most spinal cord injuries in humans come from contusions, which inherently cause more widespread and indiscriminate

damage. Neuromodulation therapies with electrical stimulation have restored function to paralyzed limbs in cut SCI models in the past; a new paper demonstrates efficacy in a contusion model now as well.

The hind limbs of the rodents used in the study were completely paralyzed following a controlled impact to the lumbar spine. Neurons below the injury were electrically and/or pharmacologically stimulated, and the animals underwent two months physical therapy with a special harness to help bear their body weight. All animals that received both forms of stimulation regained use of their hind limbs. Even though the immediate neuronal projections at the contusion site remained damaged, alternative pathways from the brainstem were activated during the rehabilitation period. De-activating those signals inhibited recovery. *EPN*

<https://doi.org/10.1038/s41684-018-0060-5>

MICROBIOME

Oxidants as antibiotics

Nat Commun. **9**, 975 (2018)

Environmental stresses during development, such as exposure to reactive oxygen species (ROS), may lengthen life span. This effect has been attributed by some to upregulation of genes that encode antioxidant enzymes and stress response genes. Alex Gould of The Francis Crick Institute and colleagues exposed developing *Drosophila* to low doses of tert-butyl hydroperoxide (tBH), which increases ROS. The adults had longer lifespans, but they did not show any sign of heightened long-term adaptive stress response. Instead, the exposed animals had a greater proportion of *Lactobacillus plantarum* in their gut, and less of *Acetobacter aceti*. The former are linked to longer life and reduced reproductive success. The results suggest that tBH has a selective antibiotic effect on *A. aceti* in larval *Drosophila*. *JK*

<https://doi.org/10.1038/s41684-018-0059-y>

Jim Kling, Ellen P. Neff

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