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In This Issue

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Unconventional muscle pain signaling

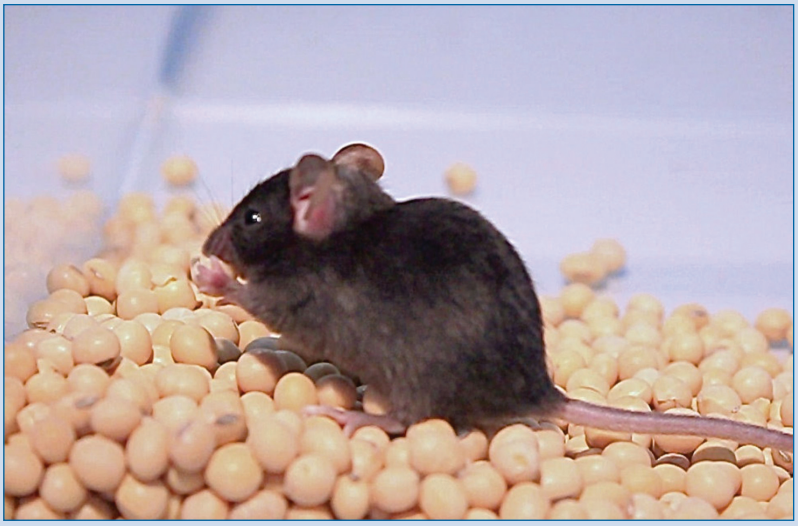


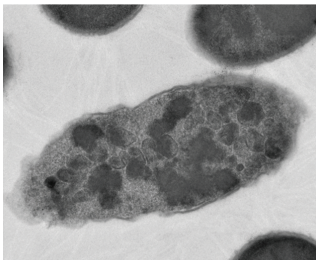
Image courtesy of Chia-Wen Wong (Institute of Zoology, National Taiwan University) and Wei-Li Wu (Institute of Biomedical Sciences, Academia Sinica).

Substance P can be inhibited by a known isoflavone isolated from soybeans.

Substance P (SP) is a pain neurotransmitter that helps excite and transmit pain signals from neural cells in many organs. Though high levels of SP in muscle tissues and spinal fluid are frequently associated with chronic muscle pain, the role of SP in muscle pain transmission and perception remains unclear. Chia-Ching John Lin et al. (pp. 363–364) used mice that lacked SP signaling to test how SP contributes to muscle pain sensitivity. The researchers found that in contrast to the neurotransmitter's usual excitatory role, mice without SP signaling showed increased pain sensitivity after intramuscular acid injections compared with mice that had normal SP signaling. Increased sensitivity to muscle pain was noted in mice lacking the gene for SP signaling as well as mice administered compounds designed to bind SP receptors. The finding suggests that SP may inhibit pain sensitization in muscle pain receptors, and may be present in patients with chronic muscle pain as part of an inhibitory feedback loop. The researchers caution that drugs designed to reduce neural reception of SP in fibromyalgia patients—currently in clinical trials—may increase patients' risk of chronic muscle pain and muscle pain sensitivity. — J.M.

Producing a carbon-fixing organelle in *E. coli* using only 10 genes

In bacteria, proteinaceous complexes known as microcompartments segregate and catalyze metabolic processes in a manner akin to organelles in eukaryotic cells. Although researchers have determined that bacterial microcompartments (BMCs) are formed from thousands of proteins arranged in complex geometric structures, little is known about how these structures self-assemble in vivo. Walter Bonacci et al. (pp. 478–483) report that a functional carboxysome—a CO_2-fixing BMC used widely as a model system for self-assembly—can be produced in *Escherichia coli* using genes from *Halothiobacillus neapolitanus*, an organism in which all 10 of the genes that encode the carboxysome reside in a single region of the genome. In addition, previous studies have shown that the carboxysome in *H. neapolitanus* can be genetically manipulated to yield empty yet morphologically well-formed shells, suggesting that self-assembly of the BMC is a self-contained, or modular, process. According to the authors, expressing the carboxysome from *H. neapolitanus* produced complexes in *E. coli* that were structurally sound and capable of both self-assembly and CO_2 fixation in vitro. The findings, according to the authors, lay the groundwork for better understanding the functional complexity of BMCs and potentially engineering synthetic self-assembling biological structures. — T.J.



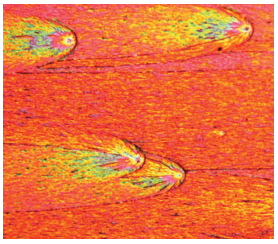
Electron microscopy images of carboxysomes in vivo.

Linking the circadian clock and immunity

Humans and animals follow a circadian cycle, with clock genes regulating a variety of daily processes. Major immune molecules produced by macrophages vary according to the time of the day, as do the symptoms of many inflammatory diseases including rheumatoid arthritis. Julie Gibbs et al. (pp. 582–587) explored the enigmatic molecular mechanisms linking the circadian clock and immunity. The authors studied the responses of mouse immune signaling proteins, called cytokines, to a bacterial toxin at different times of the day, and found that the activation of a subset

of proinflammatory cytokines varied strongly with the circadian cycle. Disrupting a key clock gene in mouse macrophages eliminated both this daily variation in cytokine response and the circadian cycles of macrophages, suggesting that daily variations in proinflammatory cytokine responses are mediated by the macrophage clock. The researchers found that they could regulate the production and release of proinflammatory cytokine IL-6 without affecting the macrophage clock, by either genetically or pharmacologically modifying the expression of a gene called *rev-erbα*. According to the authors, *rev-erbα* may play a key role in linking the circadian clock and immune function. — S.R.

Fast fracture from tiny cracks



Conic-like markings on polymethylmethacrylate broken at high speed.

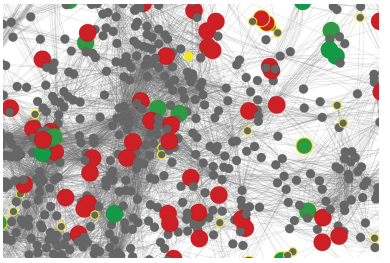
According to conventional fracture mechanics, tiny cracks slow breakage in a brittle material by blunting the tip of a large, advancing crack. However, recent experiments with polymethylmethacrylate (PMMA), a glass-like polymer, indicate that microcracks sometimes make large cracks grow faster. Claudia Guerra et al. (pp. 390–394) assessed how microcracks affect fracture in brittle materials by examining fracture surfaces after forcing cracks in PMMA. Though cracks propagate too fast to catch the process in action, PMMA microcracks leave characteristic marks on the edges of broken surfaces, the researchers note. The researchers examined the pattern of cracks on the surface of broken PMMA and used computer simulations to determine the series of events that led to the observed patterns. The results suggest that large cracks grow through the coalescence of microcracks, which form and grow at a constant rate to speed up material fracture. According to the authors, the findings directly contradict the traditional understanding of microcracks' role in brittle material fracture. The authors suggest that other brittle materials—including rocks, bones, and other types of glass—likely also experience dynamic brittle fractures. A better understanding of how fractures occur could help researchers build tougher, safer materials in the future, according to the authors. — J.M.

Improved drug screening with microdroplets

Primary drug discovery screens of large chemical libraries typically assess only a single dose of each compound, resulting in high numbers of false positives and false negatives. Promising compounds are later characterized in dose-response analyses, but time and cost usually limit the analyses to 7–10 data points, producing error-prone results. Oliver Miller et al. (pp. 378–383) developed a microfluidics system that generates precise dose-response data with approximately 10,000 data points per compound. The device produces a concentration gradient of each compound in a stream of buffer, which is then combined with the target enzyme and a fluorogenic substrate. The mixture is segmented into microdroplets that contain varying concentrations of the compound and a fixed amount of enzyme and substrate, and enzyme activity is then monitored by fluorescence. The authors screened a library of 704 compounds for inhibition of protein tyrosine phosphatase 1B (PTP1B), a potential drug target for diabetes, obesity, and cancer. The screen identified a compound that, according to the authors, is at least 10-fold more potent than the best inhibitor previously identified by screening similar compound libraries. Analysis of a known PTP1B inhibitor further revealed that with increasing concentration, the compound first activates PTP1B before achieving inhibition—a complex, biphasic dose-response relationship that would be difficult to discern from a 10-point analysis and impossible to determine from a single-point screen. According to the authors, the findings pave the way for improved methods of high-throughput drug discovery. — N.Z.

Obesity, IBD-related topologies in the human gut microbiome

Numerous microbial communities, known collectively as the human microbiome, inhabit sites in the human body and impact human health. Comparative analyses of microbiomes have revealed that the species and gene compositions vary considerably, and that certain changes in composition may be linked to disease. Sharon Greenblum et al. (pp. 594–599) devised a systems biology framework for studying the microbiome that examines the topologies, or configurations, of community-level metabolic networks contained in metagenomic data. Focusing on the human gut, the authors analyzed previously published fecal metagenomic data from 124 unrelated individuals and six twin pairs and their mothers, who had been classified as lean, overweight, or obese. Additionally, 25 of the participants had been diagnosed with inflammatory bowel disease (IBD). According to the authors, the analysis identified topological features that correlate to obesity and IBD, suggesting that these diseases may be associated with characteristic deviations from the manner in which the microbiome is normally organized. Although the associations do not imply a specific mechanism for these complex and poorly understood diseases, the authors report, the findings demonstrate an approach for studying how the microbiome functions as a whole. Furthermore, the technique could potentially help identify biomarkers for specific diseases, according to the authors. — T.J.



Community-level metabolic network of the gut microbiome; obesity-associated enzymes shown as larger colored nodes.