CHANNELS

GRASPing CFTR

Cell **146**, 746–760 (2011)

The most common mutation responsible for cystic fibrosis, which is called Δ508-CFTR, results in protein misfolding, retention in the endoplasmic reticulum (ER) and degradation of an otherwise functional channel. Gee *et al.* report an unconventional trafficking pathway for Δ508 that is dependent upon Golgi reassembly stacking proteins (GRASPs). The authors showed that conditions associated with ER stress resulted in plasma membrane localization of core-glycosylated Δ508 in cultured cells. The authors blocked conventional ER-to-Golgi trafficking pathways by genetic or chemical means, but neither type of manipulation inhibited the surface localization of functional Δ508. GRASPs, which may be involved in the stacking of Golgi cisternae or the linkage of stacks into a continuous ribbon, have recently been shown to mediate unconventional protein transport. The authors found that knockdown of GRASP abolished unconventional trafficking of Δ508-CFTR. Interaction of Δ508-CFTR with GRASP55 as well as phosphorylation of GRASP55 at Ser441 were important for the unconventional pathway. Overexpression of GRASP55 in transgenic mice rescued growth defects and improved the survival of mice harboring the Δ508-CFTR mutation. These data provide insight into an unconventional protein-trafficking pathway and suggest that activating this pathway could be a therapeutic strategy for the treatment of cystic fibrosis. *AD*

OLFACTION

A DEET-induced confusion

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The mechanism by which the insect repellant *N,N*-diethyl-*meta*-toluamide (DEET) functions remains unclear, but possibilities include interference with the olfactory system to block odor recognition or activation of olfaction to elicit avoidance. To distinguish between these models, Pellegrino *et al.* tested the effects of DEET on the electrophysiological responses of four *Drosophila melanogaster* olfactory sensory neurons (OSNs) to ten attractive odors. Different OSNs express distinct odorant receptors (ORs) that consist of a common coreceptor, Orco, and variable OR subunits that confer odor selectivity. Depending on the OSN, DEET either suppressed odor-mediated inhibition or decreased odor-induced activation. Interestingly, the odors 1-octen-3-ol and 1-octanol had opposing effects on neurons of the same olfactory hair: they inhibited the neuron expressing Or59b as the variable OR subunit and activated the one expressing Or85a. DEET inverted these responses, leading the authors to hypothesize that DEET acts as a molecular 'confusant' by scrambling the odor code via direct modulation of ORs. Further study of the Or59b–Orco complex suggested two odor-binding sites: a high-affinity site modulated by DEET and a low-affinity site insensitive to DEET. Finally, they found a *D. melanogaster* strain harboring a mutation that renders Or59b insensitive to inhibition by odor ligands and modulation by DEET, providing further evidence that DEET functions by directly interacting with ORs and alters fine-tuning of the insect olfactory system. *MB*

BIOSYNTHESIS

Finding pheofungins

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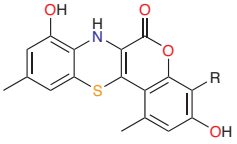

Fungi produce a diverse pool of secondary metabolites, but genome sequencing analysis has revealed that fungi have far more silent biosynthetic gene clusters than active ones. Recent studies have uncovered mechanisms that induce cryptic biosynthetic gene clusters and thus offer approaches for identifying new natural products. Scherlach *et al.* now identify the pheofungins, a new class of natural products from *Aspergillus nidulans*. The authors generated *A. nidulans* strains with mutations in protein N-acetyltransferases, which acetylate the N terminus of many eukaryotic proteins. A strain containing a mutation in the gene nidulans N-acetyltransferase B (*nnaB*) had a red-orange color in culture, unlike the typically yellow wild-type strains. Metabolic profiling of the Δ*nnaB* strain revealed that it produces a variety of phenolic carboxylic acids based on orsellinic acid and a series of red compounds. Characterization of this compound class, which the authors termed pheofungins, revealed that they contain a fused benzopyran-benzothiazinone scaffold that has not previously been seen in fungi but shares structural similarities to pheomelanins, a class of pigments found in red human hair and bird feathers. Profiling experiments revealed that pheofungin biosynthesis requires orsellinic acids and cysteine. Though its biological function remains unclear, pheofungin production is triggered by intracellular stress induced by defective N-terminal protein acetylation, suggesting that targeting other post-translational modifications is most likely a promising route for natural product discovery. *TLS*

PROTEIN FOLDING

Gamers see the solution

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Researchers have created several online games in attempts to harness efforts from the general public to advance scientific knowledge, but it is often difficult to quantify exactly what is gained from these efforts. In Foldit (http://fold.it/), players attempt to identify low-energy structures for protein sequences using both computational tools and their own three-dimensional acuity. Now Khatib *et al.* report the specific success of Foldit players both in a protein-structure prediction competition (CASP9) and in solving the structure of a protein *de novo*. In CASP9, Foldit players took on challenges in several categories including template-based modeling, template-free modeling and refinement. In template-free modeling, the Foldit Void Crushers group improved a structure generated by the Rosetta Server to generate a near-native conformation of *Pseudomonas aeruginosa* protein T0581 as determined by comparison to the subsequently released structure. The Foldit community provided a bigger surprise in a second 'real-world' challenge. Although there is crystallographic data available for the Mason-Pfizer monkey virus retroviral protease monomer, molecular replacement and other strategies have been unable to phase the data, frustrating scientists for more than a decade. After Khatib *et al.* issued a call for help, the Foldit Contenders group returned a model that could be used to solve the crystallographic data, yielding a final refined structure within a few days. *CG*

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