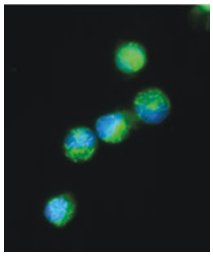
COVER STORY

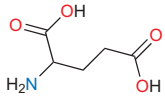
Caspase-3 serves as a key enzyme in apoptosis where signals from two distinct pathways converge, and beyond which the decision for apoptosis is irreversible. Normally, upstream proteins in these pathways initiate cell death by cleaving procaspase-3 to generate the active enzyme. Putt *et al.* have identified PAC-1, a small molecule that directly activates procaspase-3, thereby bypassing the early steps in the apoptosis machinery. This molecule is active *in vitro*, *in vivo* and against tumors in mice. The compound has particular relevance to treating cancer, as many cancerous cell lines contain mutations within the apoptosis cascades that allow uncontrolled growth. Putt *et al.* further show that procaspase-3 is upregulated in many cancer lines, which means that cancer cells may be treated with PAC-1 at concentrations that do not affect healthy cells. Because PAC-1 efficacy correlates with intracellular procaspase-3 concentrations, this compound may be well suited for applications in personalized therapy, in which procaspase-3 concentrations can be individually assessed. [**Articles, p. 543; News & Views, p. 509**] *CG*

Pump up the frataxin volume



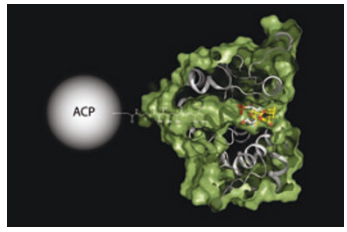
The expansion of GAA·TTC repeats in the intron of the gene encoding frataxin causes the neurodegenerative disease Friedreich's ataxia, in part by leading to a markedly decreased expression of frataxin. The ability to upregulate frataxin would be a useful starting point in treating the disease. Herman *et al.* have identified a class of histone deacetylase inhibitors that reverse the silencing caused by the triplet expansion. The authors first found that histones associated with the expanded frataxin introns are hypoacetylated and trimethylated (characteristics that are both hallmarks of heterochromatin), thereby providing an explanation for the silencing of frataxin in Friedreich's ataxia. The authors then generated a new histone deacetylase inhibitor that stimulates the acetylation of histones associated with the gene encoding frataxin, potently and specifically increasing the gene's expression. This compound now joins the handful of therapeutics that activate specific gene transcription in a human disease. [**Articles, p. 551; News & Views, p. 512**] *MB*

Profiling nitrogen metabolism



Recently developed techniques such as metabolic flux profiling have provided researchers with quantitative methods for tracking metabolic pathways in living cells. These experimental data, when combined with computational methods such as flux-balance analysis, have contributed to an enhanced understanding of metabolic pathways and the effects of environmental perturbations on these systems. Yuan *et al.* now report a new method called kinetic flux profiling that measures the forward flux of labeled nitrogen through cellular biosynthesis. The amino acids glutamate and glutamine are central hubs of nitrogen metabolism in cells. Using LC-MS, the authors characterized the assimilation of ^{15}N-labeled ammonia in *Escherichia coli* and showed that nitrogen accumulation in glutamate seems to occur via a route that is more energetically costly than the one predicted by current models. In addition to analyzing cells under normal conditions, the study offers a new approach to analyzing the ways external agents and environmental factors may affect cellular metabolism. [**Brief Communications, p. 529**] *TLS*

Curling up with polyketides



The macrolide antibiotics pikromycin and methymycin are polyketides that are formed through the stepwise sequence of initiation, elongation, reduction and macrocyclization. The final step is carried out by pikromycin thioesterase (Pik TE), one of four enzymes in the modular pikromycin polyketide synthase. Pik TE has a natural substrate tolerance, as it can generate 12- and 14-membered ring macrolactones. Acting much like a serine hydrolase, Pik TE catalyzes both the last elongation step during synthesis of the linear polyketide chain and the subsequent cyclization. Fecik, Smith and co-workers generated affinity labels for Pik TE that mimic the pikromycin heptaketide chain elongation intermediate and inactivate the enzyme's active site. Because the covalent inhibitors formed relatively stable tetrahedral intermediates, the authors could solve the co-crystal structures. From these structures, the authors were able to determine that Pik TE does not have the 'oxyanion hole' that is typical of serine hydrolases because there is a need to accommodate both ends of the polyketide, which are joined by the enzyme. The structure (based on a relatively short affinity label) also showed that there is no obvious induced-fit closing of the enzyme, which may explain the substrate tolerance of the enzyme. Co-crystal structures that included longer affinity labels revealed that the enzyme contains a wall of water in the substrate channel at an appropriate distance from the catalytic site; this wall promotes cyclization because the ends of the hydrophobic substrates curl together to avoid the water. Together, these results reveal the basis of an unconventional substrate-recognition process and provide a means to engineer novel, pharmaceutically important compounds. [Letters, p. 531, 537; News & Views, p. 511] *MB*

Prenylating proteins

A portion of proteins in eukaryotic cells are post-translationally modified by prenylation. Attachment of the hydrophobic prenyl group can be followed by proteolysis, methylation and palmitoylation. Together these modifications function to anchor proteins to membranes and control the movement of proteins between different cellular compartments. In a Review in this issue, Gelb *et al.* discuss the mechanisms of prenyltransferase and postprenylation enzyme reactions, the biological processes modulated by these modifications, and opportunities for therapeutic intervention by inhibiting these enzymes. [**Review, p. 518**] *JK*

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