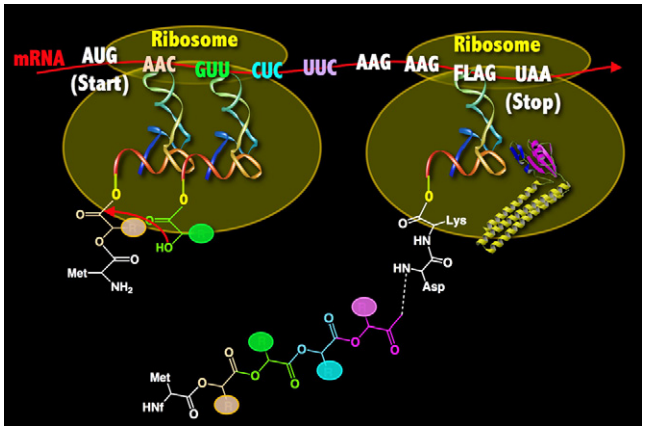
In This Issue

High Fidelity Ribosome Expression of α-Hydroxy Acids Polyesters



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In this issue, Ohta et al. report the ribosomal polymerization of α-hydroxy acids by means of genetic code reprogramming. The flexizyme system, a ribozyme-based tRNA acylation tool, was used to reassign individual codons to seven types of α-hydroxy acids. Next, polyesters were synthesized under controls of the reprogrammed genetic code using a reconstituted cell-free translation system. The sequence and length of the polyester segments were specified by the mRNA template, indicating that high fidelity ribosome expression of polyesters was possible. This work represents an exciting, not previously described example of mRNA-directed synthesis of polyesters consisting of several different α-hydroxy acids (Figure credits: Ohta et al.).

Gain-of-Function Mutational Activation in AARSs

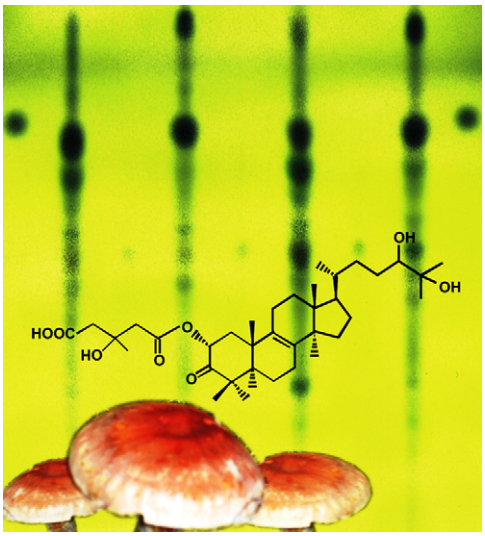
PAGE 1323

Aminoacyl tRNA synthetases (AARS) are a group of enzymes that catalyze the first step of protein biosynthesis, a formation of a covalent bond between a specific amino acid and its corresponding transfer RNA (tRNA). In addition, the idea of functional expansion of AARSs in higher eukaryotes has been emerging, suggesting a connection between these enzymes and numerous signal transduction pathways. The work by Yang and colleagues now investigates the mechanism of activation of an expanded tyrosine tRNA synthetase function. The results shed new light on why mutations in genes for tRNA synthetases, not disruptive for synthetase activity, are causally linked to human diseases and demonstrate that disease-associated mutations result in gain-of-function.

Squalene Epoxidase in Biosynthesis of Clavaric Acid

PAGE 1334

Clavaric acid is an antitumor agent of substantial pharmacological interest produced by the basidiomycete (mushroom) *Hypholoma sublateritium*. The production of this promising antitumor agent is currently limited by the low yield of the natural *Hypholoma* isolates. Godio et al. now provide evidence that clavaric acid is derived from an isoprenoid pathway; more precisely, from squalene. The authors identify and characterize a gene encoding squalene epoxidase. Microbial overexpression of this gene leads to clavaric acid overproducer strain and represents a first step in eliminating limitations of calvaric acid availability. (Figure credits: Godio et al.)



Brain 2-Arachidonoylglycerol Hydrolase Profiling

PAGE 1347

The endocannabinoid signaling molecule 2-arachidonoylglycerol (2-AG) acts at cannabinoid receptors to regulate a diverse array of physiological processes. 2-AG levels in the central nervous system are tightly regulated by enzymatic biosynthesis and degradation, but these pathways have yet to be completely elucidated. In this study, Blankman et al. adopted a functional proteomics approach to comprehensively profile 2-AG hydrolases in the mouse brain. Their results designate monoacylglycerol lipase (MAGL) as a principal 2-AG hydrolase in the mouse brain and identify two previously uncharacterized enzymes, ABHD12 and ABHD6, that also possess this activity.

In This Issue

Inhibition of Monoacylglycerol Lipase in Intact Brain Neurons

PAGE 1357

The *N*-aryl carbamate URB602 is an inhibitor of monoacylglycerol lipase (MGL), a serine hydrolase involved in the biological deactivation of the endocannabinoid 2-arachidonoylglycerol (2-AG). Using purified recombinant MGL and intact brain neurons, King and colleagues demonstrate the selective inhibitory effects of URB602 on MGL activity. The authors further show that this inhibition occurs through a partially reversible, noncompetitive mechanism using an approach that combines kinetic, dialysis, and structure-activity relationship (SAR) analyses. Thus, URB602 remains a useful tool to investigate the roles of 2-AG and validate MGL as a pharmacological target.

From Targeting Gravitropism to Understanding ABC Transporters

PAGE 1366

P-glycoproteins (PGPs) are ATP-binding cassette (ABC) transporters that translocate a myriad of molecules across biological membranes. In plants, a few PGP proteins together with PIN proteins transport the plant hormone auxin and participate in the physiological changes required for the response to gravitropic stimuli. Using a genetic and biochemical approach, Rojas-Pierce et al. identified PGP19 as a target of the gravitropic inhibitor Gravacin in *Arabidopsis thaliana*. The authors analyzed the effect of Gravacin on the transport activity of PGP19 and PGP19-PIN complexes, as well as the physical interaction between Gravacin and PGP19-containing microsomal membranes. Better understanding of the Gravacin/PGP19 system might lead to a better understanding of ABC transporters, in general. (Photo credits: Rojas-Pierce et al.)

New Way to Build a Double Hot-Dog

PAGE 1377

Eukaryotic fatty acid megasynthases utilize a dehydratase to catalyze one of the ß-carbon processing reactions that follow each chain extension step. Expression, mutagenesis and structural modeling studies by Pasta et al. suggest that the dehydratase of the animal megasynthase has evolved from a freestanding, prokaryotic, homodimeric counterpart that exhibits a typical double hot-dog fold, with two active-sites located at the subunit interface. However, in this megasynthase, the double hot-dog is formed by two "pseudosubunits" derived from contiguous regions of the same polypeptide, and only one active site is retained. This architecture differs from that of fungal megasynthase dehydratases, even though the enzymes utilize similar catalytic mechanisms.

Emetine Regulates *Bcl-x* Splicing

PAGE 1386

Emetine, the ipecac alkaloid, has been used for treatment of different human disease for centuries. More recently, it was established that emetine acts as a eukaryotic protein synthesis inhibitor. Moreover, emetine has been evaluated as a potential chemotherapeutic agent. However, molecular details of emetine mechanism of action are still lacking. Boon-Unge et al. present evidence that emetine regulates alternative splicing of exon 2 in the *Bcl-x* gene, leading to a decrease in the amount of anti-apoptotic Bcl-xL and an increase of proapoptotic Bcl-xS protein levels. Interestingly, authors show that emetine exerts the effects on *Bcl-x* splicing in a phosphorylation-dependent manner, with protein phosphatase-1 mediating these effects. Specific control of the alternative splicing of *Bcl-x* gene is an emerging target for anti-cancer treatment, and emetine is a new piece that starts to complete the puzzle.