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863 Membrane trafficking: Arls squeeze the fat out
Roger L Williams
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PERSPECTIVE
865 Lessons and revelations from biomimetic syntheses
M Razzak & J K De Brabander

By seeking to replicate either specific biochemical reactions or the chemical logic employed by cellular machinery, biomimetic synthesis serves to both inform and test proposals for natural product biosynthesis as well as expand and redefine the rules of organic chemistry.

ON THE COVER
RNA
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The impossible hexamer
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REVIEW ARTICLE

876 Choosing an effective protein bioconjugation strategy
N Stephanopoulos & M B Francis

The large number of available chemical strategies to modify biomolecules can be overwhelming and time-consuming if adopted without careful consideration. Applying chemical logic to select context-dependent protocols can streamline this process substantially, leading to a wealth of functionalized materials for use in biology and materials science.

BRIEF COMMUNICATIONS

885 N6-Methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO
G Jia, Y Fu, X Zhao, Q Dai, G Zheng, Y Yang, C Yi, T Lindahl, T Pan, Y-G Yang & C He

N6-Methyladenosine is an abundant nucleoside in cellular mRNA that undergoes demethylation under physiological conditions by fat mass and obesity-associated protein (FTO). This new pathway suggests that RNA modifications can be reversible and potentially have an impact on RNA metabolism.

888 A natural prodrug activation mechanism in nonribosomal peptide synthesis
D Reimer, K M Pos, M Thines, P Grün & H B Bode

Cleavage of peptide precursors is well known for ribosomally produced sequences. Investigation of xenocoumacin biosynthesis now points to a similar function in nonribosomal peptide synthesis for this antibiotic and for other biosynthetic clusters, explaining one source of mismatches between genetic and chemical information.

891 Dafadine inhibits DAF-9 to promote dauer formation and longevity of Caenorhabditis elegans

Dafadines, identified in a screen for compounds that induce the dauer phenotype in C. elegans, also promote longevity in adult worms, with both phenotypes occurring through inhibition of DAF-9, a cytochrome P450 involved in the insulin signaling pathway.

ARTICLES

894 α-ketoglutarate coordinates carbon and nitrogen utilization via enzyme I inhibition
C D Doucette, D J Schwab, N S Wingreen & J D Rabinowitz

Cells must coordinate nutrient uptake for balanced growth, but the mechanism by which this occurs was unknown. Flux measurements and biochemical assays now identify α-ketoglutarate as the key signal in this process that accumulates upon nitrogen limitation and inhibits an enzyme involved in glucose transport.
902 Efficient discovery of anti-inflammatory small-molecule combinations using evolutionary computing

An evolutionary algorithm predicts anti-inflammatory drug combinations that have synergistic effects on IL-1β expression more efficiently than would empirical approaches of testing drug combinations individually.

909 GPCRs regulate the assembly of a multienzyme complex for purine biosynthesis
F Verrier, S An, A M Ferrie, H Sun, M Kyoung, H Deng, Y Fang & S J Benkovic

GPCRs are known to initiate a variety of signaling pathways, but their full reach in coordinating cellular events is unknown. Live cell imaging using label-free and fluorescence assays to monitor the effects of GPCR ligands now surprisingly connects GPCR networks to nucleotide metabolism.

916 Structural basis of p38α regulation by hematopoietic tyrosine phosphatase
D M Francis, B Różycki, D Koveal, G Hummer, R Page & W Peti

NMR and ITC are used to define essential features of a p38α phosphatase interface that extend beyond the classic KIM binding site, and SAXS analysis software, incorporating NMR chemical shift data, are developed and applied to build a model of the p38α-HePTP complex.

925 Identifying polyglutamine protein species in situ that best predict neurodegeneration

Conformation-specific antibodies and longitudinal tracking of individual neurons in situ identifies a toxic monomer species linked to Huntington’s disease.

935 A de novo peptide hexamer with a mutable channel
N R Zaccai, B Chi, A R Thomson, A L Boyle, G J Bartlett, M Bruning, N Linden, R B Sessions, P J Booth, R L Brady & D N Woolfson

Coiled-coil assemblies have served as a rich resource for testing fundamental principles of protein structure and function. A semi-empirical design strategy now yields the first parallel hexamer, which also displays an internal channel that can be manipulated to direct assembly.
Cofactor mobility determines reaction outcome in the IMPDH and GMPR (β-α)$_8$ barrel enzymes


IMPDH and GMPR have similar active sites, but their reactions cause opposite effects on the guanine nucleotide pool. biochemical and crystallographic evidence point to cofactor conformation as distinguishing the two reaction mechanisms and demonstrate that GMPR can substitute for IMPDH, prompting further investigations of this metabolic cycle.

Arl2-GTP and Arl3-GTP regulate a GDI-like transport system for farnesylated cargo


Trafficking G proteins between membranes is essential for their signaling activity. Structural and biochemical studies on the farnesylated G protein Rheb and the guanine nucleotide-dissociation inhibitor (GDI)-like PDEδ suggest an allosteric mechanism for Rheb release and identify a bona fide GDI-displacement factor (GDF).

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