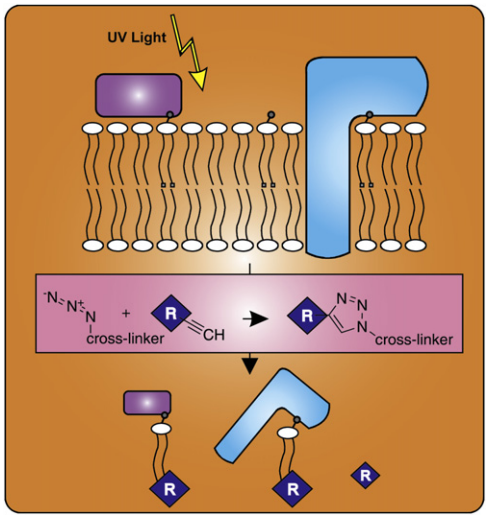
In This Issue

Photocross-linking and Clicking in the Membrane



PAGE 3

Membrane proteins are notorious for being underrepresented in proteomics studies. Gubbens et al. now describe a photocross-linking approach for capturing membrane proteins that bind to lipids at the membrane interface. They synthesize short chain lipid analogs mimicking phosphatidylcholine equipped with a photoactivatable moiety attached to the headgroup and azide-modified acyl chains for detection by click chemistry. These probes were incorporated in yeast inner mitochondrial membrane and photoactivated. Cross-linked proteins were purified and identified by mass spectrometry, which resulted in detection of both previously established and potentially new interaction partners of phosphatidylcholine. (Figure adapted from Gubbens et al.)

GSK-3 in ESCs: Enhancing Self-renewal

PAGE 15

Pluripotent embryonic stem cells (ESCs) have the ability to differentiate into all cells comprising the adult organism, making ESCs attractive for use in regenerative medicine and drug development. Understanding the mechanisms that control ESC self-renewal (proliferation with suppression of differentiation) is critical to enabling expansion of pluripotent cells. Glycogen synthase kinase 3 (GSK-3) has been implicated in control of ESC pluripotency and differentiation. To clarify its role, Bone et al. adopted a chemical genetics approach. The study demonstrates that inhibition of GSK-3 enhances self-renewal of murine ESCs, facilitating their expansion rather than promoting differentiation, and provides new tools for future investigations.

Glycosyltransferase to and from Natural Products Biosynthesis

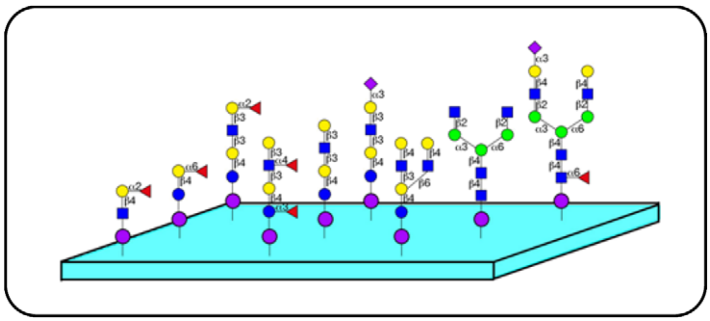
PAGE 28

As glycosyltransferases (GTs) found in nature often show distinct substrate specificity, GT engineering is an attractive area of research from both fundamental and applied points of view. Krauth et al. now report introduction of a new activity into a GT involved in natural product biosynthesis. This was achieved by identifying hot-spot amino acids involved in determining substrate specificity and conducting a systematic study of GT iterative action, an activity unique to GTs involved in biosynthesis of natural products. This work provides a foundation for the design of GTs with engineered substrate specificity and the development of diverse glycosylated natural products.

Natural Glycan Microarrays Zoom In

PAGE 36

Glycomics research reveals that cells and tissues from every organism generate diverse, distinctive glycan repertoires. The most successful strategy to characterize carbohydrate interactions employs glycan microarrays of chemically synthesized glycans. However, chemical synthesis alone provides limited libraries of known structures amenable to current synthetic mechanisms. Large, complex glycan libraries will only be available from naturally occurring glycans immobilized on glycan microarrays. Song et al. describe a method for rapidly and quantitatively derivatizing glycans from natural biological sources. The approach is applied to explore intrinsic molecular glycan recognition by galectins, uncovering interesting features of differential glycan recognition. (Figure adapted from Song et al.)

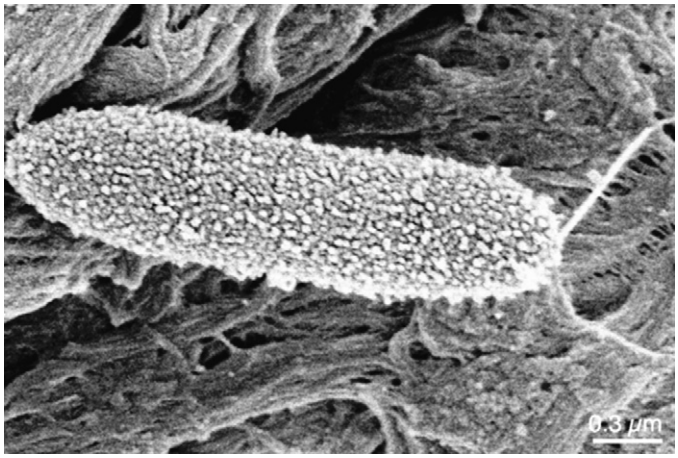


Src Activity, Membrane Microdomains, and Cytoskeleton

PAGE 48

Membrane microdomains function as segregated signaling platforms. In the report by Seong et al., FRET-based Src biosensors were tethered in or outside of lipid rafts (one kind of microdomain at the plasma membrane) to study regulation of Src kinase in different membrane microdomains. The process of Src activation in rafts was found to be slower and weaker and dependent on actin. In contrast, Src activation in non-rafts was faster and stronger and dependent on microtubules. Hence, Src is differentially regulated via cytoskeleton at different membrane microdomains. This report highlights the utility of developed FRET-based, membrane-targeted biosensors for investigating enzymatic activity within different plasma membrane compartments.

Surface-Tethered Cationic Peptides Antibacterial Jabbing



PAGE 58

Prosthetic-associated infections represent one of the most serious complications in orthopedic surgery, and although antibiotics do demonstrate efficacy in such cases, they are only effective for reducing the rate of early infections. Compounding these concerns is the reduced effectiveness of prophylactic antibiotics due to antibiotic resistance. The use of surface-tethered cationic antimicrobial peptides on medical devices represents an intriguing alternative strategy that combines direct antimicrobial activity with negligible induction of microbial resistance. Here, Hilpert et al. introduce a high-throughput screening methodology and perform structure activity relationship studies for assessment and optimization of surface-tethered antimicrobial peptides. (Figure adapted from Hilpert et al.)

Unusual Chemistry in Chondrochlorens Story

PAGE 70

Myxobacteria often perform unusual chemistry to assemble a wide variety of natural products with useful therapeutic activities. The study by Rachid et al. focused on unravelling details of biosynthetic pathways for production of antibiotic chondrochlorens A and B in *Chondromyces crocatus*. Besides providing information on number of enzymes with the role in these pathways, authors identified a unique radical SAM enzyme involved in the bacterial secondary metabolism that catalyzes the methylation of an unreactive methyl moiety of a methoxy group and a candidate catalyst for an uncommon oxidative decarboxylation reaction.

Glycerol Monomycolate is a Mycobacterial Lipid Antigens

PAGE 82

The role of CD1-restricted, lipid-specific T lymphocytes during *Mycobacterium tuberculosis* infection is an important issue, since these cells might participate in protection. *M. tuberculosis* envelope contains an extraordinarily high lipid content with wide molecular diversity. Although mycobacterial lipids with different structures stimulate CD1-restricted T cells, their relative contribution to specific immunity during infection is unknown. Here, Layre et al. describe a novel mycobacterial lipid antigen, glycerol monomycolate (GroMM), which is presented by CD1b and stimulates $CD4^+$ T cells. The findings describe the rules of GroMM immunogenicity and its contribution to anti-*M. tuberculosis* repertoire in infected patients.

Matrix Metalloproteinases in Melanophore Migration

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Matrix metalloproteinases (MMPs) are a family of secreted Zn^{2+}-dependent endopeptidases involved in degradation and cleavage of protein components of an extracellular matrix. Tomlinson et al. used a chemical genomic approach with developing *Xenopus laevis* embryos to identify a novel matrix metalloproteinase (MMP) inhibitor. Using this inhibitor along with complementary loss-of-function of MMP-2 and 14, they show that MMPs are necessary for in vivo melanophore (pigment cell) migration. These results have implications not only in the context of developmental biology, but they also have significance in understanding the role of MMPs in the processes of cellular migration and cancer. (Figure adapted from Tomlinson et al.)