In This Issue

Small Molecule Inhibitors of Protein SUMOylation

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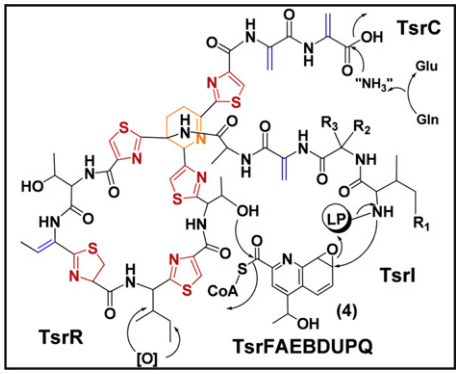
SUMOylation is a posttranslational protein modification by SUMO, a small ubiquitin-like modifier protein. Deregulation of SUMOylation or deSUMOylation processes can have a severe impact on cellular fate and lead to serious physiological outcomes. Fukuda et al. now report specific inhibition of SUMOylation by small molecules, ginkgolic acid, and its analog, anacardic acid. These compounds inhibit protein SUMOylation both in vitro and in vivo, without affecting ubiquitination, through direct interaction with E1, leading to inhibition of the E1-SUMO intermediate formation. These findings could spark future development of chemical tools for investigating the roles of SUMO in a variety of cellular pathways and therapeutics against diseases involving aberrant SUMOylation.

Insight into Thiopeptide Biosynthesis



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The biosynthetic pathways of thiopeptides, which contain a characteristic macrocyclic core with multiple thiazoles, dehydroamino acids, and a 6-membered nitrogen heterocycle, remain elusive. Here, Liao et al. establish a common pathway for thiopeptide biosynthesis featuring ribosomally synthesized precursor peptides and conserved posttranslational modifications by cloning, sequencing, and characterization of the thiostrepton and siomycin A gene clusters. The generality of biosynthetic scheme is supported by genome mining and confirmed by the thiocillin I production in a strain that was previously unknown as a thiopeptide producer. The pathway is remarkably concise and efficient and its tailoring could be a very attractive strategy to access thiopeptide structural diversity. (Figure adapted from Liao et al.)

Polypeptide Backbone Photocleaved!

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Ability to photocleave a polypeptide backbone at a specific site could represent a universal method to control and regulate functional peptides and proteins with high spatial and temporal resolution. Peters et al. now demonstrate that 2-nitrophenylalanine can be both biosynthetically incorporated into polypeptides and induced to cleave polypeptide backbone upon light irradiation. The photocleavege reaction yields a C-terminal carboxylate group and an unusual N-terminal cinnoline group. The authors suggest that methodology will be useful for generating biologically active species from inactive precursors.

Site-Specific Tyrosine Sulfation in Chemokine Story

PAGE 153

Sulfation of tyrosine is a common posttranslational modification of proteins that plays critical roles in numerous physiological and pathological processes. Studies of tyrosine sulfation have been hindered by the difficulty of introducing sulfate groups at specific positions of peptides and proteins. Simpson et al. describe a general, efficient, and readily automated method for synthesis of peptides containing sulfotyrosine at one or more specific position(s). Experiments using sulfopeptides generated by this method show that the position of sulfation is critical in controlling the interaction of the chemokine receptor CCR3 with the proinflammatory chemokine eotaxin.

Gypsy Moth: Chemical Language of Love

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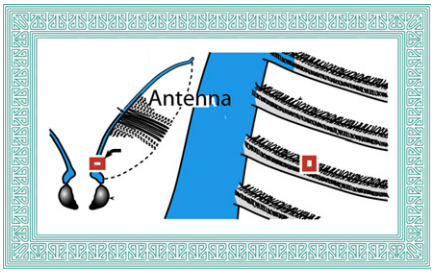
Insects base many important choices, such as mate finding, on chemical signals. These signals are detected by specialized sensory hairs, which contain odorant-binding proteins. Gong et al. have found that an odorant-binding protein from the gypsy moth binds the sex attractant pheromone in two steps. The first step is a collision between an external site on the protein and pheromone. The second step is movement of the pheromone to an internal binding site that is gated by the C-terminus of the protein. The second step contributes to the selectivity and may be the key to correct identification of the pheromone by the moth. (Figure adapted from Gong et al.)



RNA Aptamer Induces Transcription

PAGE 173

Hunsicker et al. have identified an RNA aptamer which is able to activate transcription of the bacterial transcriptional regulator TetR by modulating its DNA-binding activity. Thereby, the aptamer displays similar activity in vivo as the natural inducer tetracycline. The aptamer was found by a combined approach of in vitro selection for TetR binding and in vivo screening for TetR induction. Due to its small size, high-induction efficiency, and the stability of the TetR aptamer under in vivo conditions, it is well suited to be an alternative RNA-based inducer of TetR-controlled gene expression. (Figure adapted from file provided by Hunsicker et al.)

Ethylenediamine-Scaffold Inhibitors of Protein Farnesyltransferase

PAGE 181

Protein farnesyltransferase (FTase) is an enzyme that catalyzes an attachment of farnesyl groups to cysteine residues of more than 60 proteins involved in intracellular signaling networks. Development of small-molecule FTase inhibitors has been pursued as an anti-cancer and antimalarial strategy. In order to further the design of a potent and selective anti-malarial FTase inhibitor, Hast et al. employed X-ray crystallography to solve structures of complexes of mammalian FTase with five inhibitors, two of which exhibit more than 1000-fold selectivity towards *P. falciparum* FTase inhibition. The structures highlight features of both the inhibitor and enzyme that control binding and selectivity, thus suggesting opportunities for further selectivity improvement of future generation of antimalarial inhibitors.

Fumagillin and Fumarranol to Combat Malaria

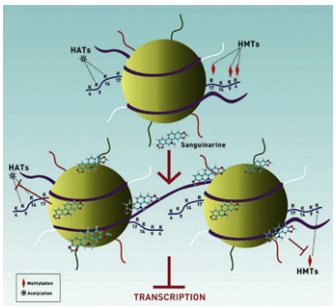
PAGE 193

Malaria is one of the leading causes of death in the developing world, and the discovery and development of novel antimalarial drugs is essential for the control of malaria infection. It has been reported that fumagillin, a natural product that inhibits angiogenesis through inhibition of human methionine aminopeptidase (hMetAP) 2, possesses potent antimalarial activity in vitro. Chen et al. now develop a mammalian three-hybrid system and use it to demonstrate the direct interaction between fumagillin and *Plasmodium falciparum* MetAP2. Furthermore, they demonstrate that analogs of fumagillin are active against malaria in an animal model *in vivo*.

Sanguinarine Modulates Epigenetic Modifications and Transcription

PAGE 203

Sanguinarine (SGR) is a benzylisoquinoline alkaloid found in a number of traditional medicinal plants with diverse cellular effects. Here, Selvi B. et al. investigate SGR interaction with chromatin and establish that besides exhibiting its previously described function as DNA intercalator, SGR binds core histones and induces chromatin aggregation. This dual binding property of SGR leads to inhibition of core histone modifications, such as specific histone methylation and acetylation. Although it does not affect in vitro transcription from a DNA template, SGR represses acetylation-dependent chromatin transcription. SGR-mediated repression of epigenetic marks and the alteration of chromatin geography modulates global gene expression. (Figure provided by Selvi B. et al.)



Essential Redox Switch In Yeast Demystified

PAGE 217

Oxidation of key cysteine residues to sulfenic (RSOH) acid is observed in a growing number of proteins from aerobic organisms and is proposed to regulate a wide variety of phenomena including signal transduction. Paulsen and Carroll provide the first direct evidence that cysteine oxidation to sulfenic acid is essential for the activation of a vital oxidative stress-sensing switch in yeast. Their results shed light on the growing roles of sulfenic acid modifications in biology and highlight the utility of cell-permeable, small-molecule probes to investigated redox-regulated signal transduction in living cells.

Alternative Routes to Actinorhodin Biosynthesis

PAGE 226

Actinorhodin has attracted considerable attention because of its vivid blue pigmentation, which allows a convenient detection of antibiotic production, and served as one of the most studied model compounds for understanding the biosynthesis of aromatic polyketides and the regulation of their production. In this study, Okamoto et al. reveal a unique situation in which two alternative routes for quinone formation are available for the later tailoring steps of actinorhodin biosynthesis. Oxygenation, including quinone-formation and hydroxylation, is one of the key steps in secondary metabolism, so these findings may have wide significance for understanding and manipulating the oxygenation of a variety of aromatic compounds.

