acs chemical biology

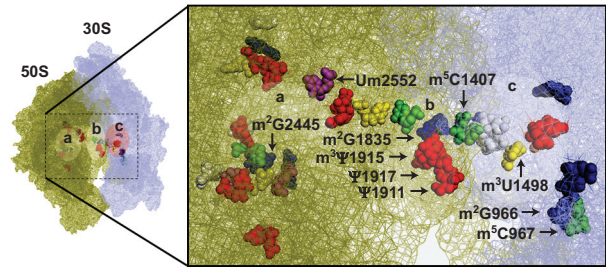
In this ISSUE

A Circular Display

Protein–protein interactions direct many key cellular processes and are enticing, albeit challenging, targets for drug design. The signaling protein Gαi1 participates in several distinct interactions with other proteins, including the Gβγ heterodimer, cell-surface G-protein-coupled receptors, and downstream effector proteins. In their search for Gαi1-binding molecules that could disrupt these interactions, Millward *et al.* (p 625) combine the power of phage display technology, the increased stability of cyclic peptides, and the enhanced diversity of an expanded genetic code to create a trillion-member cyclic peptide library.

Phage display libraries were strategically designed to enable incorporation of the unnatural amino acid *N*-methyl phenylalanine and, in a final step of the synthesis, cyclization with a cross-linking reagent to connect the N-terminus to a fixed lysine residue. Seven rounds of selection against Gαi1 resulted in the clear emergence of core motifs within the macrocyclic structure important for binding. In addition, detailed characterization of one of the identified peptides revealed significantly increased binding affinity and enhanced proteolytic stability relative to the linear peptide. This approach could be applied to the creation of other low-molecular-weight, high-affinity ligands for protein surfaces.

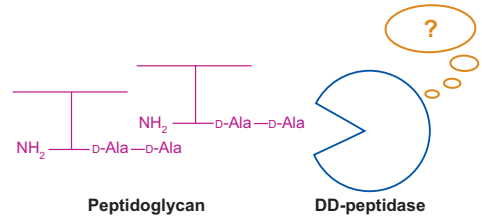
More than Four RNAs



Post-translational modifications of proteins have captured much attention over the last several years because of their vital roles in the regulation of protein activity. Receiving significantly less consideration have been the >100 post-transcriptional modifications that occur on RNAs. Chow *et al.* (p 610) review recent evidence implicating these somewhat neglected modified nucleosides in the modulation of important aspects of ribosome structure and function, including the protein translation process, ribosome stability, and antibiotic sensitivity.

Modifications of the four standard RNA nucleosides can be classified into four main categories: isomerization of uridine to pseudouridine; base alterations such as methylation, deamination, reduction, thiolation, or alkylation; methylation of the ribose 2′-hydroxyl; or more complex modifications such as multiple modifications. Notably, in the ribosome, these modifications tend to occur in functionally important regions, such as those dedicated to peptidyl transfer, the polypeptide exit tunnel, and the intersubunit bridges. This, coupled with the fact that ribosomes containing unmodified RNAs are less stable and less able to carry out protein synthesis than native ribosomes, suggests that the chemical diversity added by the RNA modifications likely enables fine-tuning of interactions that stabilize ribosome structure and facilitate ribosome function. In addition, it is known that specific ribosomal RNA modifications, especially methylation, can affect a cell's sensitivity to certain antibiotics. Given that the ribosome is a target for many antibiotics, understanding the role of RNA modifications in the interactions between ribosomes and antibiotics could aid in the design of new antibiotics that are not susceptible to resistance mechanisms.

Searching for Substrate Specificity



For more than three-quarters of a century, the penicillin family of β-lactam antibiotics has championed the fight against bacterial infections, and today they remain the most widely used antibiotics. Despite this impressive history, surprisingly little is known about the substrate specificity of their targets, the penicillin-binding proteins (PBPs). PBPs catalyze a key final step in the biosynthesis of the bacterial cell wall, the cross-linking of the peptidoglycan polymer. In an attempt to elucidate how these enzymes recognize their substrates, Kumar *et al.* (p 620 and Point of View p 603) explore PBP reactivity in an *in vivo* setting.

Using several strains of bacteria and membrane extracts containing PBPs, the authors compare the activity of β-lactams containing peptidoglycan structures designed to mimic those present in the bacteria under examination with that of generic β-lactams. Intriguingly, the specific PBPs did not appear to recognize elements of peptidoglycan structure adjacent to the reaction center. Given the complexity of the environment surrounding cell wall biosynthesis, the authors conclude that other elements must contribute to substrate recognition. These studies offer valuable insight into the design of new antibiotics.

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