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In This Issue

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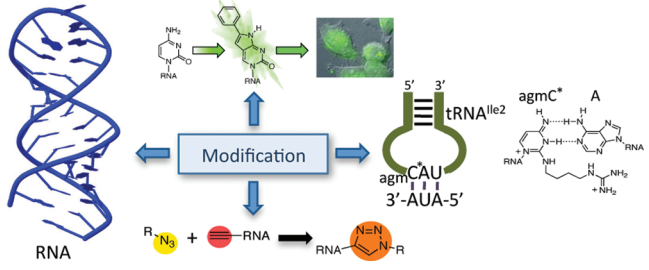
PROBING RNA, NATURALLY AND SYNTHETICALLY

The incredibly diverse activities of RNA, such as controlling gene expression, catalyzing reactions, and participating in cell signaling processes, are regulated in part by naturally occurring structural modifications that impart specific functions to the RNA. In addition, synthetic modifications to RNA provide tools with which to explore RNA function. Phelps *et al.* (DOI: 10.1021/cb200422t) now review the various natural and synthetic structural modifications to RNA and discuss how these alterations inform our understanding of RNA function.

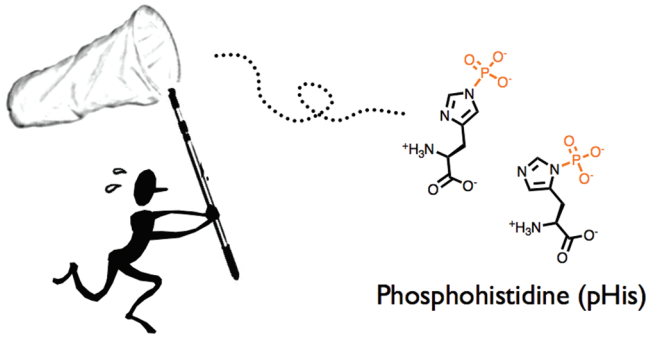


Incorporation of synthetic modifications to RNA, which include spectroscopic tags such as fluorescent molecules and labels for nuclear magnetic resonance, and addition of reactive handles like alkynes or azide groups that facilitate site-specific modification, are valuable approaches for probing RNA function. Discovery of naturally occurring modifications, like addition of a methyl group or nicotinamide adenine dinucleotide, or transformation of cytosine to agmatidine, have offered complementary insight into RNA function. Further development of novel synthetic methods for modifying RNA and innovative approaches to investigate the naturally occurring RNA modifications will continue to enhance our understanding of this fundamental biomolecule.

PHOSPHO SIBLING RIVALRY

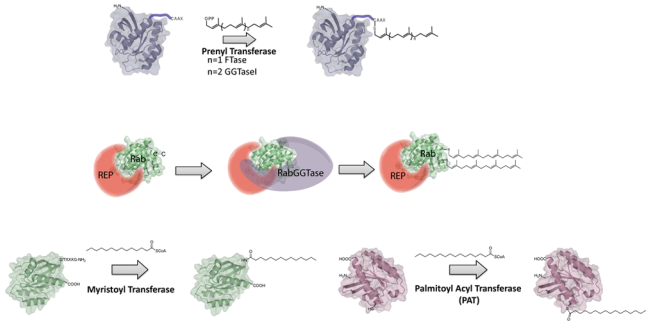
Studies of protein phosphorylation, a cornerstone event in cellular signaling processes, are dominated by exploration of serine, threonine, and tyrosine modification, despite the fact that six other amino acids are known to be phosphorylated. Though most well characterized in plants and microorganisms, histidine phosphorylation occurs in higher eukaryotes, and evidence suggests it may play a bigger role in biology than currently appreciated. Kee and Muir (DOI: 10.1021/cb200445w) now offer an intriguing glimpse into phosphohistidine biology and review recently developed tools and approaches that will pave the way for deepening our understanding of this elusive modification.

One reason for the lack of appreciation of histidine phosphorylation may be technical in nature. Its inherent instability makes it difficult to detect, and a lack of appropriate techniques and reagents has made it difficult to characterize. However, new tools such as improved mass spectrometry methods and antibodies that specifically recognize phosphohistidine will greatly facilitate investigation into histidine phosphorylation and begin to level the playing field for exploration of protein phosphorylation events.



INHIBITING LIPIDATION

Many cellular signaling events depend on the transmission of signals from outside the cell to inside. Signaling proteins present in the cell membrane function as liaisons between these two worlds, but not all such proteins have explicit transmembrane domains. Those that do not are often posttranslationally modified by lipid groups, which direct their localization to the cell membrane and thus plays an important role in their function as signaling molecules. Specific enzymes are



responsible for protein lipidation, and inhibition of this process may have therapeutic implications, as many lipidated signaling proteins are mutated in human cancers. Triola *et al.* (DOI: 10.1021/cb200460u) now review progress in the development of small molecule inhibitors of lipidation enzymes.

The numerous classes of lipidation enzymes, including farnesyl transferase, geranylgeranyl transferase I and II, N-myristoyltransferase, and S-acyl transferases, as well as the delipidation enzymes called acyl protein thioesterases, have offered unique opportunities for development of small molecule inhibitors. In addition to their therapeutic potential, various inhibitors of the lipidation and delipidation processes have proven valuable tools for deciphering the complex world of lipidation biology.

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