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Editors Letter

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Recasting Biomolecules for Function

During the holiday season, transformations abound. At the end of the year, my family, friends, and colleagues parade in their ugly sweaters or their New Year's Eve party-wear. I was thinking about how these adornments can influence our circle of interactions. As a tangible example, my colleague George Phillips attracted a crowd with his prize-winning sweater (Figure 1). Our first issue of 2012 also focuses on transformations—specifically, it contains reviews that describe how post-synthetic covalent modifications of biomolecules affect their interactions within the cell.

Figure 1. Pictured from left to right: Aaron Hoskins, John Markley, George Phillips, Laura Kiessling.

Powerful analytical tools, especially mass spectrometry methods, are revealing that cells carry out a panoply of post-synthetic reactions. That cellular catalysts chemically elaborate the structures of nucleic acids, proteins, glycans, and lipids has long been known. Indeed, post-translational modifications of proteins, including proline hydroxylation and phosphorylation, were first identified in the early 1900s.[1−3] Thus, while modifications of proteins have been known for over 100 years, researchers are still elucidating the mechanisms by which they influence protein function and cellular decisions. Moreover, we now appreciate that nucleic acids and glycans also are subject to post-synthetic transformations. Indeed, the number of distinct types of covalent modifications is mounting, and the important functional consequences of these changes are fueling research in fields from microbiology to immunology to epigenetics.

The topics in our review issue highlight how the discipline of chemical biology is advancing our understanding of cellular post-synthetic transformations. The types of modifications described in the different reviews are wide-ranging, as are the physiological consequences of each modification. Still, the chemical biology approaches employed have some common features.

Noted in almost all of our reviews is the development and application of synthetic methods to install defined modifications at specific sites within the molecule of interest. Applications of protein assembly or modification methods are highlighted in the review by Wang and Lomino, which describes elegant methods to install specific oligosaccharides at target sites within a protein,[4] and the excellent contribution of Strieter and Korasick, which includes an overview of methods to generate ubiquitin conjugates of defined regiochemistry and polyubiquitin conjugates of defined lengths.[5]

As mentioned in the introduction, a major benefit of access to specifically modified biomolecules is that the influence of the modifications on their binding partners can be discerned. Phelps *et al.*, provide several examples of how modifications in RNA influence specific interaction partners, including how siRNA modifications can yield agents that avoid activation of the innate immune response yet retain their ability to promote RNA interference.[6] Muthana *et al.* offer insights into how post-synthetic modifications of glycoconjugates influence their recognition partners and thereby processes that range from host−pathogen interactions to inflammation.[7]

New enzymatic, chemoenzymatic, or chemical syntheses have been developed to generate substrates to unravel the specificity and mechanisms of modifying enzymes. McCusker and Fujimori describe advances in our understanding of the intriguing mechanisms of the enzymes that mediate antibiotic resistance by ribosome modification.[8] In addition, the Strieter review highlights how access to ubiquitin conjugates has advanced our understanding of the specificity of select enzymes that carry out ubiquitination. The fascinating review by Nabel *et al.* on cytosine modification underscores the importance of defining the substrate specificity of different modifying enzymes. It also delineates the questions regarding how cells interconvert different cytosine derivatives.[9]

Chemical biology also has afforded new strategies to detect and quantify modifications within the cell. Kee and Muir note that the lability of phosphorylated histidine residues complicates monitoring them, and they highlight how chemical biology approaches are providing new strategies to detect and analyze histidine phosphorylation.[10] One of the approaches is to generate antibodies to nonhydrolyzable analogues. This ability to generate stable analogues of different post-synthetic modifications is a major advantage. The use of stable yet non-natural biomolecule derivatives is also described in many of this month's contributions, including those by the Kohli, Beal, Strieter, and Wang groups.

The use of small molecules to block a target protein or process is a hallmark of chemical biology. This approach takes center stage in the contribution by Triola *et al.* on protein lipidation.[11] Their review highlights a variety of strategies that have been used to identify small molecules that block enzymes that mediate the attachment of different lipids to proteins. The theme of using small molecule inhibitors is one also taken up in the reviews by Gildersleeve and Fujimori groups.

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Together, the reviews in this issue emphasize how biopolymers can be recast for different uses. Some post-synthetic processing events are highly dynamic (*e.g.*, histidine phosphorylation), while others are longer lasting (*e.g.*, sulfation of glycosaminoglycan chains). Whether highly dynamic or more static, each type of modification provides the cell with a frugal means for diversifying its response to its environment. Although we have known that biomolecules are modified for over 100 years, researchers are continuing to uncover new and unexpected changes to nucleic acids, proteins, lipids, and glycans. Though predictions around the new year can be dangerous, I need not go out on a limb to project that chemical biology will make major contributions to our understanding of the chemistry underlying post-synthetic modifications and the biological consequences that result.

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