Editorial

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Editorial on Chemical Tools in Glycobiology

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Chemical tools have proven indispensable for studies in glycobiology. Synthetic oligosaccharides and glycoconjugates provide materials for correlating structure with function. Synthetic mimics of the complex assemblies found on cell surfaces can modulate cellular interactions and are under development as therapeutic agents. Small molecule inhibitors of carbohydrate biosynthetic and processing enzymes can block the assembly of specific oligosaccharide structures. Inhibitors of carbohydrate recognition and biosynthesis can reveal the biological functions of the carbohydrate epitope and its cognate receptors. Carbohydrate biosynthetic pathways are often amenable to interception with synthetic unnatural substrates. Such metabolic interference can block the expression of oligosaccharides or alter the structures of the sugars presented on cells.

Collectively, these chemical approaches are contributing great insight into the myriad biological functions of oligosaccharides. Oligosaccharides and glycol conjugates (glycoproteins and glycolipids) have intrigued biologists for decades as mediators of complex cellular events. With reference to structural diversity, they need the capacity to far exceed proteins and nucleic acids. This structural variance allows them to encode information for specific molecular recognition and to function determinants of folding, stability, and pharmacokinetics. Given that glycosylation is one among the foremost biquitious sorts of posttranslational modification, the unexpectedly small number of genes identified within the initial analyses of the human genome sequence provides even more impetus for understanding the biological roles of oligosaccharides. Oligosaccharide functions are now being elucidated in molecular detail, but advances in glycobiology are slow to arrive compared with the pace of revelations in protein or macromolecule biochemistry. The same structural diversity that has captivated biologists has also frustrated efforts to define oligosaccharide expression patterns on proteins and cells and to correlate structure with function.

Some technical challenges are analytical in nature; determination of the oligosaccharide sequence on a selected glycoconjugate remains faraway from routine. Others originate from glycol conjugate biosynthesis, which is neither template-driven nor under direct transcriptional control. Oligosaccharides are assembled in step-wise fashion primarily in the endoplasmic reticulum and Golgi apparatus, a process that affords significant product micro heterogeneity. As a result, it's difficult to get homogeneous and chemically defined glycol conjugates from biological sources. Without such materials in hand, biological functions are difficult to unravel. Genetic approaches have contributed considerably to our appreciation of oligosaccharide function. The availability of entire genome sequences has revealed the multiplicity of enzymes that contribute to glycol conjugate assembly. Their deletion in model organisms has provided substantial insight. For example, mice deficient during a mannosidase II expressed an altered portfolio of N-linked glycans on their cell surface glycoproteins. The mice were susceptible to a systemic autoimmune response, suggesting that abnormalities in N-glycosylation in humans could also be an element within the pathogenesis of autoimmunity. Still, cell surface presentation of straightforward also as complex glycans requires many genes to be expressed together, which complicates the analysis of single gene “knockouts” or “knockins.”

Access to structurally defined oligosaccharides and glycol conjugates may be a prerequisite for unraveling their function. Chemical routes to the assembly of oligosaccharides are, therefore, essential. Advances on this front are providing materials for the assessment of glycan function, the establishment of the structural features important for function, the elucidation of biosynthetic pathways, the creation of carbohydrate-based vaccines, the assembly of non-natural glycosylated antibiotics, and therefore the generation of inhibitors of glycol conjugate function.