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Introduction: Glycobiology—Understanding the Language and Meaning of Carbohydrates

The ability to decipher nature's most enigmatic alphabets, that of the carbohydrate sequences that are present in many eukaryotic cell proteins, has led to an explosion of interest in the possible exploitations of this discovery. Having read the sequence, the problem now becomes 'what do we do with this information?' Some of the solutions can be found in this special Glycobiology issue, devoted to an understanding of the basic science and functional issues surrounding protein glycosylation.

In the opening article, Roth gives the precise role of glucose residues transiently attached to N-linked oligosaccharides and of a specific high-mannose-type oligosaccharide. The relevance of these moieties in protein recognition events in the endoplasmic reticulum in protein folding identifies the importance of this process in health and disease. This process is conserved in all eukaryotic species and emphasizes a crucial role of glycosylation. The functional significance of distinct cell surface oligosaccharides in cancer is demonstrated further and highlights their importance in cell−cell interactions.

The potential to create proteins that contain a large and diverse number of oligosaccharides, glycoforms, is regulated by cell- and tissue-specific enzymes found in the endoplasmic reticulum and Golgi apparatus. Does an understanding of their structure lead to explanations for their roles at the cell surface? Ritchie and colleagues provide an analysis of glycosylation of proteins in the complement system. They suggest that the roles for glycans are more than just a structural stabilization of the protein and protection from proteolytic degradation. The differential glycosylation observed may modulate enzyme activity in the complement cascade ensuring the fidelity of protein/protein interactions.

The fine detail found in an oligosaccharide sequence requires usually more than one method for analysis. Mechref and Novotny give a comprehensive review of the tools at our disposal for structural determination of N- and O-linked oligosaccharides with high sensitivity. A strategy is developed to provide sequence and linkage information additional to gross 'fingerprinting' of the glycoprotein. With a complete assignment of structure, it is possible to determine the conformation and dynamics of oligosaccharides and glycoproteins as Wormald and colleagues describe. When several complementary approaches were applied to the study of a particular biological problem, glycopeptide recognition by the MHC, the affinity of peptide/protein interactions could be partially understood. Further clues for function come from an understanding of the interaction between carbohydrate binding proteins, lectins, and their cognate binding partners.

Dam and Brewer comprehensively review the use of isothermal titration calorimetry (ITC) for estimating lectin binding thermodynamics and understand their biological function. Lectins often recognize monosaccharide residues, alone or as part of an extended structure. Two reviews describe the occurrence, biosynthesis, and regulation of residues identified in several eukaryotic species. The first is by Zachara and Hart, who describe the protein modification by O-linked GlcNAc, which is thought to modify their functional activity. Several lines of evidence support an analogous role of this modification to protein phosphorylation in cellular regulation. All eukaryotic species analyzed contain O-GlcNAc-modified proteins in contrast to their lack in prokaryotes. This hints at some evolutionary divergence in glycosylation potential, and Angata and Varki expand this theme in the second review. Sialic acid is found in several bacterial and eukaryotic species, and a phylogenetic analysis predicts a possible early origin of the sialic acid biosynthesis pathway, despite the fact that only higher animals of the deuterostome lineage consistently show the presence of this sugar. The interplay between species, particularly that of host/pathogen, may play some part in the inheritance of survival factors that include sialic acid. The use of carbohydrate mimetics has been developed to exploit this, and as Kiefel and von Itzstein report, chemical modification of sialic acid has therapeutic potential. The design of inhibitors to sialic acid-recognizing proteins, either biosynthetic or hydrolytic enzymes or lectins, generates tools for manipulating viral infections, inflammatory disease, and cancer.

The diverse structural complexity of carbohydrates can also be manipulated by chemists to generate a

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large library of compounds for exploitation as pharmacological agents. Gruner and colleagues review the synthesis and application of sugar amino acids as versatile building blocks for the preparation of unnatural oligomers ('foldamers') and biologically active mimetics of peptides and oligosaccharides. The discovery and use of imino sugar inhibitors has had a considerable impact on the potential treatment of viral diseases, non-insulin-dependent diabetes, cancer metastasis, and Gaucher disease. Lillelund and colleagues in a thorough evaluation of inhibitory constants of transition-state analogues describe the chemistry of synthetic glycosidase inhibitors.

To increase the affinity of weak carbohydrate/protein interactions, for example, lectin binding, to those affinities required to mediate physiologically significant processes, multivalency is required. Lundquist and Toone review methods for the synthesis of polymeric platforms and analyze the effect of cluster formation on ligand binding. They identify the molecular features required for an effective strategy for inhibiting the pathology associated with bacterial recognition and adhesion. The ability to synthesize chemically glycoproteins with complex structures also leads in to an opportunity to intervene therapeutically in a number of physiological processes, including microbial pathogenicity. Davis reveals some of the strategies adopted by carbohydrate chemists to achieve these goals and leaves us with an intriguing question. How can we accurately predict the carbohydrate alphabet so that both chemists and biologists can keep pace with the technologies in the genomic age? The wealth and quality of information found in this special issue will not give us easy answers but provides a firm foundation for future directions.

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