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Putting glycobiology on a structural footing

Editorial overview

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Carbohydrates and their conjugates represent the largest and most varied class of biological macromolecules. While protein and DNA are stuck with their linear arrangement of a limited repertoire of monomers, sugars can be linked to each other (or proteins, lipids) through a range of linkages giving rise to a bewildering and confusing set of tree-like molecules. Consequently the mechanisms of glycan synthesis or their interaction with specific proteins have been difficult to study at the atomic level. This, at least partially, explains why glycans and the biology linked to them (glycobiology) have been largely ignored, where possible, by the average biologist.

This issue describes several areas of glycobiology where rather dramatic developments in the past 2–3 years have uncovered the molecular basis of a number of important biological processes. Not only have exciting new structures been solved, but many of these also have been exploited to generate specific inhibitors that will encourage further biological studies in a range of cellular systems.

Henrissat *et al.* describe some of the recent landmarks in the structural biology of glycosidases and glycosyltransferases, with sharp focus on some of the surprises that these findings unearthed. Particular attention is paid to the novelty (structurally and mechanistically) of such work, with the caveat that the glycobiology community can expect the unexpected as genome sequencing adds to the carbohydrate-active enzyme database (CAZy, www.cazy.org).

Although the precise enzymatic steps involved in the synthesis of peptidoglycan in the bacterial cell wall have been pieced together decades ago, the molecular mechanism of the synthesis of the polymer from lipid monomers was not understood until recently. The review by Lovering *et al.* discusses this synthesis at the membrane interface, combining evidence from the two recent X-ray structures of peptidoglycan glycosyltransferases with other advances in the field. Alongside their exciting potential as antibacterial targets, these enzymes are central to our relatively new appreciation of the complexity of bacterial physiology—the review details the potential contribution of the structures to both areas of research and it appears we may even be close to understanding the structure of the wall itself!

Strikingly, virtually nothing is known about the structures and mechanisms of the rather large, membrane embedded enzymes that processively synthesize the fungal cell wall 'equivalents' of bacterial peptidoglycan—glucan and chitin. We hope that these challenging enzymes will be tackled by some courageous structural biologists in the next decade.

Solving structures 'by proxy' is an approach routinely used by structural biologists to overcome difficulties with expressing eukaryotic targets. An (apparent) orthologue for the eukaryotic gene of interest is identified in the prokaryotic kingdom and is generally easily expressible using routine approaches, leading to improved chances of obtaining diffraction quality crystals. This approach was long believed to be impossible for the eukaryotic enzymes involved in *N*-glycosylation/*O*-glycosylation in the secretory pathway owing to a lack of clear bacterial orthologues. The contribution by Abu-Qarn *et al.* shows that this is no longer true. In particular the reconstitution of functional *N*-glycosylation in *E. coli* using a *C. jejuni* gene cluster opens a new avenue for gaining insights into the structures of the enzymes involved in eukaryotic *N*-glycosylation.

The 'dwarf' of the glycan field, *O*-linked *N*-acetylglucosamine (*O*-GlcNAc), was discovered more than two decades ago. The past five years have seen many studies reporting important biological consequences of this modification, including examples of how it may compete with protein phosphorylation. Hurtado-Guerrero *et al.* summarize an explosion in our molecular understanding of the enzymes that are responsible for the dynamic and inducible nature of this intracellular modification, the *O*-GlcNAc transferase and the *O*-GlcNAcase. In just the past two years alone, crystal structures of apparent bacterial orthologues have been reported leading to biochemically testable hypotheses of how these enzymes interact with and recognize (glyco)peptide substrates. In parallel, an impressive range of potent and selective *O*-GlcNAcase inhibitors have been reported that are invaluable tools in cell biological studies of *O*-GlcNAc. What is needed now is structure determination of protein–protein/peptide complexes to understand how the hydrolase and transferase bind their substrates.

One of the problems limiting the exploitation of many interesting targets in the glycobiology field has been the relative dearth of specific inhibitors for the glycosyl hydrolases/transferases. Perhaps more importantly, the sight of a carbohydrate as a substrate to mimic with small molecule inhibitors has turned away many a medicinal chemist owing to the inherent nondrug-likeness of sugars. The contribution by von Itzstein should be an encouragement to big pharma to enter this area. Promising glyco-enzyme targets have now been identified against viral, mycobacterial, fungal and protozoan pathogens. Substrate-based sialidase inhibitors have already enjoyed widespread use as antivirals, and now these are being further developed to target the virulent H5N1 strain. Examples of sialidase, UDP-galactopyranose and chitinase inhibitors clearly show that it is possible to move away from carbohydrate-based scaffolds into areas of chemical space usually explored by the medicinal chemist.

Adhesion to human cell surfaces is an important step in pathogenic invasion. Imberty *et al.* provide details of this specific recognition event for a variety of pathogens—bacteria, viruses and parasites (*Toxoplasma*), detailing the variety utilized in the recognition of carbohydrate antigens by lectin and adhesin modules. Chemical interference of glycoconjugate binding would be of immense use in disease treatment, and structural biology can undoubtedly lead the way in inhibitor design.