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Editorial overview: Carbohydrate–protein interactions and glycosylation: integrating structural biology, informatics and systems modelling to understand glycan structure and glycan-protein interactions

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Harry Gilbert obtained his PhD from the University of Southampton in 1979 and subsequently moved to the Public Health Laboratory Service at Porton Down to develop proteins for the National Health Service using the emerging molecular biology methodologies. In 1985 he moved to a New Blood lectureship at Newcastle University with the remit of develop molecular biology approaches to livestock research. He was made a professor in 1992 and in 2003 moved to the newly formed Institute for Cell and Molecular Biosciences at Newcastle University. Apart from working in the USA from 2008 to 2010, he has remained at Newcastle. His major area of research interest is in the structure function relationships of carbohydrate modifying enzymes and non-catalytic carbohydrate binding modules. Recently he has applied his interest in the enzymology of complex carbohydrate degradation to the human distal gut commensurate bacterial community.

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Nagasuma Chandra obtained her PhD from the University of Bristol, UK for her work in the area of structural biology of enzymes and subsequently moved to the Indian Institute of Science, Bangalore to work on the structural biology of lectins, initially as a postdoctoral fellow, and subsequently starting her own research group in 1999. She is currently an Associate Professor at the Department of

Carbohydrate polymers play a critical role in biology, providing nutrients for a range of microbial ecosystems that impact on both mammals and plants. Similarly the glycosylation of proteins and lipids has a significant influence on cellular function and communication, which contributes to health and disease. From an industrial perspective, the polysaccharide cellulose is the most abundant source of organic carbon on the planet and thus represents a substrate for the energy and chemical industries, which offers a sustainable and environmentally non-toxic alternative to fossil fuels. Consequently there is considerable interest in the structure of both complex carbohydrates and the carbohydrate-active enzymes (CAZymes) that modify these polymers. In this section on carbohydrate-protein interactions and glycosylation, the articles review our current understanding of the structure and function of CAZymes and glycosylation processes using structural biology and computational biology, respectively. As a large amount of data is being gathered on various glycans and glycoforms, the need to intelligently comprehend such data and make sense of it is also increasing. As a result, a new branch of glycoinformatics has emerged, which enables comparison of glycans, identification of their variations in disease and provides an understanding of their structure-function relationships. These insights provide a rational basis to engineer desired glycoforms or desired specificities in glycan binding proteins. The complexity in terms of number of molecular players as well as in their interplay requires the use of systems biology approaches to integrate multiple pieces of data and understand how they influence each other so as to generate predictive models of processes related to glycan formation, their recognition and their downstream function.

The translocation of large sugar polymers across the outer membrane is unique to gram-negative bacteria. Here the article by Woodward and Naismith reviews recent progress in the molecular understanding of both the biosynthesis of polysaccharides at the inner membrane and their translocation across the outer membrane. The protein crystal structures have provided an atomic model of the process of synthesis to export. This unprecedented detail has not only transformed our understanding of the underlying biochemistry, which will underpin antimicrobial drug development; an urgent priority given the concerning rise of multidrug resistant organisms.

The surface of a cohort of gram positive anaerobic bacteria contain large multienzyme complexes that degrade plant cell wall polysaccharides. These enzyme complexes, termed ''cellulosomes'', are assembled by the interaction

Biochemistry, Indian Institute of Science and additionally affiliated with Bioengineering and Mathematical biology initiatives at the institute. Her contributions include elucidating structural determinants of carbohydrate recognition and genome-wide prediction of carbohydrate binding proteins. In the recent years, she has been applying systems biology approaches to study tuberculosis by using different types of molecular interaction networks at different levels from systems to protein structures which has provided an understanding of the gene essentiality in the pathogen, systems perspective of the emergence of drug resistance, molecular response networks in the host upon infection, which have lead to new potential drug combinations and combination targets.

of dockerin domains on the catalytic subunits with cohesin domains on the scaffoldin proteins. In their review Nash *et al.* highlight the structural basis for the dual binding modes displayed by dockerins for their cohesin ligands. They propose several hypotheses for the selection pressures that have led to this unusual binding mode. The article also highlights how single-molecule mechanical experiments are shedding light on the exceptional mechanical properties of cellulosome components, and how this may be exploited in the future in new technological applications relying on stable protein mechanics.

Starch is a simple polymer of α-linked glucose residues, yet a multiplicity of enzyme activities is required to degrade the polysaccharide. The review by Møller and Svensson has focussed on the crystals structures of recently discovered starch degrading enzymes and new structures for previously characterized enzymes involved in the process. This highly complex field has been summarized brilliantly, providing an excellent entry point for structural biologists interested in starch degradation. Among the several significant advances made in the field the article summarizes the structural details of the catalytic steps in plant disproportionating enzyme and the regulatory protein-protein interactions of the barley limit dextrinase.

The article by Gentry *et al.* is also focused on enzymes that modify starch and the related animal α-glucan, glycogen. The article describes the phosphatases that de-phosphorylate these glycans; Laforin targets glycogen and SEX4/LSF2 attacks starch. SEX4 and Laforin contain non-catalytic carbohydrate binding modules (CBM) that target starch. Although LSF2 lacks a classical CBM, it contains starch binding sites out with the substrate binding region that houses the active site, reminiscent of the starch degrading glycanases reviewed by described by *Møller and Svensson*. The crystal structures of these enzymes in complex with appropriate ligands reveals the molecular details underpinning the specificities displayed by these phosphatases. Intriguingly, the structural data reveal how these accessory CBMs and carbohydrate binding sites contribute to enzyme function through different mechanisms. Indeed, the CBM in SEX4 plays a direct role in substrate binding in the active site of the enzyme, revealing a unique role for such protein modules in enzyme function.

The next two articles focus on the structural basis for enzyme specificity (Attia and Brumer) and catalysis (Igarashi). The article by Attia and Brumer reviews the genomics and structural biology of xyloglucan degradation. The article compares the genomic and biochemical organization of xyloglucan degrading systems from human gut *Bacteroides* saprophytic soil gram-negative bacteria and anaerobic gram-positive prokaryotes that occupy different ecosystems. The review illustrates how these systems are organized to reflect the environment of the bacteria, exploiting the cellulosome and surface adhesion sequences in the anaerobes to ensure degradation is in proximity with the cell surface, while in gram negative prokaryotes the key endo-acting enzymes, containing appropriate CBMs are secreted into the environment. Much of our understanding of the mechanism of catalysis and substrate specificity of these endo- and bespoke exo-acting enzymes is derived from a plethora of structural information. Particular highlights include the delineation of structural features that confer both specificity for xyloglucan, as opposed to other β-1,4-glucans, and their modes of action. The review by Igarashi reveals how high resolution neutron crystallography provides novel insights into the mechanism of glycoside hydrolases. In the vast majority of these enzymes carboxylate residues mediate acid/base-assisted cleavage of glycosidic bonds. In the review, however, neutron crystallography showed that amide side chains could be in the imidic-acid

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