

# Biopolymers

## Modulation of nucleic acids, carbohydrates and proteins to different task

Editorial overview

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The world of biopolymers has seen a wealth of advances in the past year. The nine reviews in this section concentrate on the recent advances in three areas of research: carbohydrates and glycoconjugates; proteins and peptides; and nucleic acids.

Three reviews in this section emphasize the wide range of biological functions for glycoconjugates and the chemical methods that are being used to elucidate their underlying molecular basis. The first review highlights the important advances that can be made by combining chemical and biological approaches to address fundamental questions. The focus is on how the covalent attachment of saccharides to specific asparagine residues alters protein structure and function. The second and third reviews describe non-covalent protein–carbohydrate recognition events that have significant physiological consequences. In these latter two examples, physico-chemical methods are contributing to our understanding of protein–carbohydrate recognition and to the development of strategies to modulate carbohydrate function.

In the first review, Imperiali and O'Connor (pp 643–649) provide an update on the important structural and functional consequences of *N*-linked glycosylation. Although this post-translational modification of proteins is common, an understanding of how *N*-linked glycosylation affects protein structure and function is only starting to emerge. The review highlights new advances in many different aspects of chemistry and biology. Chemical and chemo-enzymatic syntheses and new methods in heterologous protein production are providing access to homogeneous samples of complex glycopeptides and glycoproteins. These newly available molecules are being used to explore the relationship between structure and function. Evaluation of these materials using thermodynamic analyses and modern structural methods is providing insight into how *N*-linked glycosylation affects the stability, folding, conformation and

dynamics of proteins. A feature common to many (but not all) of these processes appears to be the ability of *N*-glycosides to alter the entropy of the system. The review highlights the many variations on this theme: glycosylation can stabilize the folded structure by raising the energy of the unfolded state, restrict the conformational flexibility of proximal residues, or orient proteins on the cell surface. Progress in this area is accelerating rapidly, fueled by advances in chemistry and biology.

Much exciting research is ongoing in the application of synthetic glycoconjugates to evoke specific immune responses. A number of groups are exploring the design of synthetic neoglycoconjugates to elicit desired immune responses toward carbohydrate determinants displayed on specific cell types (e.g. anti-cancer vaccines). The review by Chen, Andreana and Wang (pp 650–658) focuses on complementary efforts to understand and inhibit a carbohydrate-induced immune response. Specifically, this work focuses on the critical role that carbohydrates play in organ rejection following xenotransplantation and synthetic ligand approaches to limit organ rejection. Synthetic ligands, surfaces and supports are being designed to remove the unwanted antibodies from circulation, to inhibit the action of the antibodies and to downregulate the production of specific antibodies. These applications are exciting as they could lead to a general strategy for inhibiting unwanted immune responses.

The intriguing biomechanical properties of protein–carbohydrate interactions are highlighted in the review by Lawrence (pp 659–664). Selectin–carbohydrate interactions, which facilitate leukocyte recruitment to inflammatory sites, mediate the dynamic process of leukocyte rolling along the inflamed endothelium. The unique physical and mechanical features of the selectin–carbohydrate interaction appear to be important for cell rolling. The design of parallel plate flow chambers that allow cell rolling to be monitored *in vitro* under a variety of conditions has provided critical insight into the physiological process. For example, a number of different selectin–ligand partners have been found to facilitate cell rolling, but most other receptor–ligand pairs are capable only of mediating firm adhesion. In selectin-mediated rolling, molecules that are effective inhibitors under static conditions can be inactive under conditions of flow, and the dimerization of selectin (or selectin ligand) increases its ability to mediate cell rolling. Lawrence describes the development of a model to relate mechanical force and receptor–ligand affinity, which is critical for understanding

structure and function relationships in this system. With the ability to assess the mechanical properties that contribute to cell rolling and access to defined, synthetic selectin ligands, our understanding of this important dynamic process undoubtedly will increase.

One of the most rapidly moving areas of biopolymer research is the chemical synthesis of proteins and three reviews in this section reflect this. For years, it was very difficult to synthesize chemically homogeneous proteins with lengths longer than approximately 100 residues. In the mid-90s, however, chemical ligation strategies were developed to allow ligation of chemically synthesized or bacterially expressed protein fragments. These methods have greatly expanded the availability of chemically synthesized proteins with unusual or isotopically labeled amino acids for spectroscopic and functional studies. Kochendoerfer and Kent (pp 665–671) describe the most recent innovations in this area with particular emphasis on metalloproteins and integral membrane proteins.

The emergence of strains of pathogenic bacteria that are resistant to commonly used antibiotics has reinvigorated research into the discovery and mechanism of action of natural antibiotics. McCafferty, Cudic, Yu, Behenna and Kruger (pp 672–680) review the topic of synergy and duality in the mechanisms of antibiotic peptides. Nature has crafted a myriad of natural products that disrupt bacterial DNA transcription, translation and membrane integrity. Historically, the mechanistic aspects of naturally occurring peptide antibiotics have been studied individually, one antibiotic and one function at a time. Many antibiotics, however, interact with their targets in a synergistic manner. In other cases, antibiotic-producing organisms have integrated multiple functions within a single peptide antibiotic.

The design of unnatural biomimetic polymers is an exciting recent endeavor that both tests rules of biopolymer folding and function and provides novel useful materials. Barron and Zuckermann (pp 681–687) review recent progress in this exciting field. Molecular biological approaches hold promise for the biosynthesis of unnatural proteins that assemble into complex architectures with well-defined chemical and physical properties. Chemical approaches have allowed the synthesis of unnatural oligomers that demonstrate folding, assembly and specific biorecognition. This review should stimulate further growth of this rapidly expanding field.

Finally, this section highlights new developments both in the DNA and RNA fields in three reviews. All of them describe the interaction of these nucleic acid biopolymers with various ligands that modulate their activities. The review by Dervan and Bürli (pp 688–693) deals with the design of polyamides for the sequence-specific interaction with double-stranded DNA. This interaction is based on the formation of hydrogen bonds between the polyamide and the nucleotides in the minor groove. The achievement

of sequence specificity for such an interaction is a major achievement and obviously requires a judicious choice of the composition of the polyamide. The development of this strategy has far reaching consequences for which the inhibition of transcription in cell culture is an excellent example. It heralds the application of polyamides for the study of gene function where, in particular cases, it might have advantages over the commonly used antisense oligodeoxynucleotides.

The review by Walter, Vicens and Westhof (pp 694–704) is concerned with the interaction of aminoglycosides with various RNAs. It has long been known that aminoglycosides can bind to certain RNAs but the structural and physico-chemical basis of this interaction has only recently begun to be understood. NMR studies have revealed the structural basis for the interaction of these antibiotics to the 16S ribosomal RNA, which has long been known to result in interference with the translation process. A different kind of interaction has been elucidated for catalytic RNAs whereby certain positively charged aminoglycosides displace metal ions. As these metals are often essential for the activity of the ribozymes, it is not surprising that such displacement often results in inhibition of ribozyme activity. *In vitro* selected RNA aptamers with affinities for neomycin B show similar structural folds that, however, do not necessarily require sequence homology. These studies underline the conformational flexibility of RNA to accommodate the same type of ligands.

The review by Scott (pp 705–709) is an in depth analysis of the role of metal ions in small ribozymes. Most of these require metal ions such as  $Mg^{2+}$  for optimal activity. However, whereas the hammerhead ribozyme depends on the metal's presence, the hairpin ribozyme, which catalyses an identical reaction, does not. It is generally accepted that the metal ion is essential for the formation of the catalytically competent conformation, the question is whether it has an additional function in the hammerhead: to act as a base to initiate the phosphoryl transfer reaction. Unfortunately the available X-ray crystal structures do not provide an unambiguous answer. The review therefore takes the leadzyme, obtained by *in vitro* selection, as a model to explore the role of the metal ion. Of particular interest is a  $Ba^{2+}$  localized at the cleavage site. Presumably this site could be occupied in the active ribozyme by a  $Pb^{2+}$  that would then be positioned to act as a base to initiate the reaction. This, so far, is the best evidence consistent with an active role of a metal ion in a ribozyme-catalysed reaction.

These reviews on nucleic acids are interesting examples of how this field moves forward in terms of synthetic DNA analogs and in our understanding of the role of RNA as a catalyst. Further developments in both these areas will contribute to the growing field of applying nucleic acid based drugs to sequence-specific interference with gene expression and eventually to combat diseases.