Carbohydrate Chemistry. State of the art and Challenges for Drug Development

by Laura Cipolla

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Glycobiology is the study of the structure, function and biology of carbohydrates, also called glycans, which are widely distributed in nature. They are saccharides that can be attached to a wide variety of biological molecules through an enzymatic process called glycosilation necessary to augment their function. These natural compounds consisting of carbon, hydrogen, and oxygen atoms have several roles in living organisms including energy transportation, as well as being the main structural support for plants and arthropods. When combined together to form polymers, in fact, they can function as long-term food storage molecules, protective membranes for organisms and cells, and as the main structural support for plants.

Despite the important functions of the four fundamental building blocks of life, proteins, carbohydrates, lipids, and nucleic acids, glycans have received the least attention from researchers also if, glycobiology is a rapidly growing field with relevance to biomedicine biotechnology and basic research. However, these important polysaccharides, conjugated to lipids or proteins, cover the extracellular side of most cell membranes and are involved in the majority of biological processes at the cellular level, including host defense, cell development and differentiation. Thus, the glycan composition membrane, being species-and tissue-specific, is used as a cellular post code in cell-cell and cell-pathogen recognition.

The book tries to give an overview of the key aspects of carbohydrate biology and chemistry by **19 chapters divided in 4 parts.**

Structure and Biological Function of Glycoconjugates is the topic reported of **Part 1** by the **chapters 1-3**. Glycoproteins characterized for containing one or more covalently linked glycan chains, play important biological roles. Existing widely in eukaryotic systems and in some bacteria and archea, they can serve as structural cell wall components, lubrificants, protective agents, transport molecules, inhibitors, hormones, and enzymes. For these reasons glycoproteins represent the major therapeutic proteins to produce humanized therapeutics with improved functions and homogenous forms at industrial scale. Thus, plant have been established as alternative hosts to mammalian cell lines for glycoprotein production, and recently the yeasts are successfully genetically engineered to produce human-like glycans. Chemoenzymatic glycosilation of natural and recombinant glycoproteins *in vitro* provides, in fact, an attractive approach to produce glycan-defined glycoforms. Among them gangliosphingolipids, also called gangliosides and characterized by the presence of one of several sialic acid residues in their carbohydrate moieties, are important compounds of the cell membranes. The lipid moiety of vertebrate glycosphingolipids (GSLs), for example, consists of either a sphingoid or ceramide which is a sphingoid base linked to a fatty acid through an amide bond. According to the most common way to classify them neutral, GSLs are glycolipids containing only uncharged sugars, such as glucose, galactose, or fucose as substituents on the ceramide moiety, while the acidic mojeties of GSLs (gangliosides) are those that contain ionized functional groups attached to neutral sugars, or ionizable sugar residues, such as sialic acid.

These complex compounds support different functions in tissue and cells and may change under physio-pathological conditions through a differential hydroxylation or saturation that may occur at level of the alkane chain. On one hand, most of the structural variability of gangliosides and glycosphingolipids are connected to the carbohydrate domain that exhibits a staggering structural diversity. On the other hand, lipid rafts are highly dynamic structures containing specific lipids and proteins and can be seen as critical signalling platforms for many cellular functions, such as adhesion, growth, and migration. Moreover, gangliosides serve as receptors for a large set of pathogens, including viruses, bacteria, and toxins and are involved in cell mitochondrial damage and apoptosis, and overexpressed on several types of cancer including melanoma, brain tumors, small cell lung carcinoma and breast cancer.

As part of living systems, Lipopolysaccharides (LPSs), consisting of carbohydrates and lipids, are endotoxins which activate the immune system and represent the major component of the outer membrane (OM) of almost Gram-negative bacteria and some Cyanobacteria. These endotoxins, in fact, play a key role during severe Gram-negative infection, sepsis, and septic shock.

LPSs are heat-stable amphiphilic molecules indispensable for the viability and survival of Gram-negative bacteria, contributing to the structural integrity of their outer membrane and to the protection of the bacterial envelope. The ordered structure and low fluidity of the LPS monolayers, stabilized by electrostatic interactions between divalent Ca/Mg cations and negatively charged groups present on LPS molecules, are responsible not only for the increased permeability of hydrophobic compounds and to higher molecular weight of hydrophilic compounds, but also for the bacterial resistance to external stress factors. Moreover, LPSs have been shown to be the most potent immunostimulant molecules, playing a key role in the pathogenesis of Gram- negative infections, triggering the immune system from insects to humans.

Part 2, *Towards Glycomics: Methodologies and Techniques for the Determination of the Structure and Activity Relationship*, reports the modern technologies used to elucidate and investigate the biological role of carbohydrates by the **Chapters 4-7**. The 3D structure of carbohydrates, in fact, play a pivotal role in their recognition by receptors. Thus, knowledge at the maximum resolution possible of this complex structure together with the characterization of its recognition by different entities, such as lectins, enzymes, viruses, and antibodies, is essential for a thorough understanding of many vital processes and opening the possibility of their modulation.

On one hand, NMR spectroscopy, assisted in many cases with molecular modelling protocols, provides scientists with the possibility to study in solution and atomic scale, the structure of carbohydrates and the mechanisms that govern their recognition by receptors. Thus, advances in different biophysical and spectroscopic techniques, such as X-Ray crystallography and nuclear magnetic resonance (NMR), complemented by quantitative data obtained through isothermal titration microcolorimetry (ITC), allowed for gathering information on protein-carbohydrate complexes at atomic resolution, permitting speculations on the forces involved in their interactions. On the other hand glycan, isolated from natural materials as a component of the entire glycome, became an important source for microarray preparation. However, rather than being a diagnostic device, glycan arrays can also be a valuable aid in finding antigens of diagnostic value for the subsequent production of monoclonal diagnostic antibodies used for enzyme-linked immunosorbent assay tests. Unfortunately, the rate of data production in glycomics has been rather limited, in comparison to proteomic and genomic research, but if genomic is perceived as a starting point, glycomics could be considered the end.

Part 3, *Synthetic Challenges: Towards Drug Development* reports, by **chapters 8-10**, reports some outlines on the synthetic methodologies developed to produce new oligosaccharides and glycoconjugates. The creation of the corresponding building blocks is the most time-consuming part for the complete synthesis of oligosaccharides. The first step is, in fact, the retrosynthetic analysis and the choice of the appropriate building blocks that have to be built up, before the glycosilation reactions necessary to connect the different monosaccharidic subunits. Thus, the need for simple and efficient methodologies to access structurally defined oligosaccharides, polysaccharides, and glycoconjugates. For the chemical assembly of these blocks, in fact, a repetitive series of glycosilation and tedious protection/deprotection steps result necessary.

In contrast to the complex chemical synthesis, enzymatic glycosilation offers many advantages, since enzymes provide selectivity and perfect control of the sugar substrate configuration, without the need of protecting groups. For these reasons, the enzymatic strategies are an open field of research in glycosciences and industrial biotechnology, so that new enzymes and protein engineering for novel specificities and improved performance are the today fast developing topics. In any way, to keep pace with the exploding area of glycobiology, it is critical to make complex carbohydrates more accessible to the general chemical, biochemical, and industrial audience. Expeditious strategies for oligosaccharide assembly in solution require, in fact, specialist knowledge of all the aspects of carbohydrate chemistry, fine-tuning of the reaction conditions and reactivity levels, and sophisticated and expensive synthesizers.

Part 4, *Carbohydrate-Based Compounds for Medical Chemistry Applications*, by **chapters 11-18**, reports relevant cases and opportunities for the development of therapeutics, based on carbohydrate structures. Glycosidases are involved in many important biological, processes, such as intestinal digestion, post-translational processing of the sugar chain of glycoproteins, cell-cell and cell-virus recognition, etc. Therefore, glycoside inhibitors could have great potential for the treatment of diabetes, viral infection, lysosomal storage disorders, and metastatic cancer. However in the last decade, it has become clear that sugar mimetics can be not only glycosidases inhibitors for biological effects, but can also act as immune modulators and pharmaceutical chaperones of misfolded proteins, without inhibiting glycosidases. Thus iminosugars, sugar-analogs with a nitrogen in place of the corresponding oxygen in the ring, become one of the most interesting discoveries in the fields of natural product chemistry.

The initial pharmaceutical interest in iminosugars was related to their properties as glycosidase inhibitors, while now they have been re-evaluated for the new and unexpected therapeutic applications due to their structural similarity with the corresponding sugars.

Despite the advent of antibiotics, implementation of national vaccination campaigns, and intensive care support, bacterial meningitis continues to be an important cause of morbidity and mortality among high risk groups With the exception of hygienic water, therefore, nothing has probably been more important in the history of infectious diseases and medicine than vaccines. Carbohydrates, in the form of oligosaccharides and glycoconjugates, are associated, in fact, with protein stabilization, cancer metastasis, viral host interactions, bacterial pathogenicity, and signal transduction, for their metabolic role. As matter of fact, the most common feature of the organisms, causing most of the bacterial meningitis, is a carbohydrate capsule with different oligosaccharide patterns that act as both a virulence determinant and target protective antibody. Specific antibodies acting against the bacterial surface polysaccharides may, therefore, enhance the elimination of pathogenic bacteria. Thus, the significant and recent progress in immunology, resulted in the development of several sophisticated vaccines, polysaccharide-based, which can be used against invasive bacteria and other human pathogens, for their efficacy and safeness.

Another recent progress has been the design of sophisticated antitumoral vaccines made with the aim to stimulate more specific and efficient immune responses against tumours. These synthetic vaccines are principally composed of tumor-associated carbohydrate antigens (TACAs) that are over expressed at the surface of a large variety of tumors, where they play crucial roles in invasion and metastasis processes.

In any way, glycans are not only an important source of metabolic energy, but as previously reported, are also widely expressed as glycoconjugares on the surface of cells, forming the glycocalix (dense coat of carbohydrates) that plays a key role in many biological processes. One of its key role is to recognize and translate the chemical information encoded in the sugar structures. At this purpose, lectins are the protein that recognize glycans with high specificity, so that the carbohydrate-lectin interactions are implicated in several key biological events, such as cell-cell self-recognition processes, cell-extracellular matrix interactions, cell growth, differentiation, signaling, adhesion, migration, etc. However, most lectins are multimeric so that polyvalent presentations of saccharides, acting as binding determinants for a given lectin, are used in nature to establish multivalent interactions. Thus the necessity to make glycomimetic molecules and scaffolds, capable to antagonize these lectins and improve drug-like properties, comparable to natural sugars.

According to the conclusion, reported on **Part 5** by **chapter 19** *Carbohydrate-Based Drugs on the Market: Overview and Future Directions*, the renaissance in glycobiology has led to an increasing interest towards the pathophysiological mechanisms in which carbohydrates take part, with the ultimate aim of discovering novel spots for therapeutic intervention.

Carbohydrates are providing to be promising drug, leading to cover several therapeutic niches and challenging discoveries by the creation of new structures with an incredible biological and innovative therapeutic potential. By an increased knowledge of the carbohydrate chemistry and the cell biochemistry, therefore, will be possible to industrializing new potent carbohydrate-based drugs and vaccines characterized by a high effectiveness and very low toxic side effects.

In conclusion, this interesting book, written from leading experts addresses the state of the art for drug development by the use of carbohydrate compounds. Moreover, it provides also a greater understanding of their involvement in human physiological and pathological states. Each chapter, highlighting the more recent research and development conducted in the field of chemistry, biology and therapeutic potentialities of carbohydrates, can be of help for all academic and industrial researchers, working in the faculty of chemistry or medicine, as well as students and marketing managers who wish to enter into the fascinating field of glycobiology.

P. Morganti
Editor-in-Chief