
Preface

Lectins are phylogenetically ancient proteins that have specific recognition and binding functions for complex carbohydrates of glycoconjugates, that is, of glycoproteins, proteoglycans/glycosaminoglycans, and glycolipids. They occur ubiquitously in nature and typically agglutinate certain animal cells and/or precipitate glycoconjugates without affecting their covalent linkages. Lectins mediate a variety of biological processes, such as cell–cell and host–pathogen interactions, serum–glycoprotein turnover, and innate immune responses. Although originally isolated from plant seeds, they are now known to be ubiquitously distributed in nature. The successful completion of several genome projects has made amino acid sequences of several lectins available. Their tertiary structures provide a good framework upon which all other data can be integrated, enabling the pursuit of the ultimate goal of understanding these molecules at the atomic level. With growing interest in the field of glycobiology, the function–structure relations of animal lectins have increased at an explosive rate, particularly in the last 20 years. Since lectins mediate important processes of adhesion and communication both inside and outside the cells in association with their ligands and associated co-receptor proteins, there is a need of a reference book that can describe emerging applications on the principles of structural biology of animal lectins at one point. No book has ever described in a coordinated fashion structures, functions, and clinical applications of 15 families of animal lectins presently known. Therefore, with the increasing information on animal lectins in biomedical research and their therapeutic applications, writing of a comprehensive document on animal lectins and associated proteins in the form of *Animal Lectins: Form, Function, and Clinical Applications* has been the main objective of the present work. The entire manuscript has been distributed into two volumes in order to produce an easily readable work with easy portability. Volume 1 comprises most of the superfamilies (Chaps. 1–21) of lectins, excluding C-type lectins or C-type-lectin-like domain. In volume 2, we have mainly focused on C-type lectins, which have been extensively studied in vertebrates with wider clinical applications (Chaps. 22–46).

Animal Lectins: Form, Function, and Clinical Applications reviews the current knowledge of animal lectins, their ligands, and associated proteins with a focus on their structures and functions, biochemistry and patho-biochemistry (protein defects as a result of disease), cell biology (exocytosis and endocytosis, apoptosis, cell adhesion, and malignant transformation), clinical applications, and their intervention for therapeutic purposes. The book emphasizes on the effector functions of animal lectins in innate immunity and provides reviews/chapters on extracellular animal lectins, such as C-type lectins, R-type lectins, siglecs, and galectins, and intracellular lectins, such as calnexin family (M-type, L-type, and P-type), recently discovered F-box lectins, ficolins, chitinase-like lectins, F-type lectins, and intelectins, mainly in vertebrates. The clinical significance of lectin–glycoconjugate interactions has been exemplified by inflammatory diseases, defects of immune defense, autoimmunity, infectious diseases, and tumorigenesis/metastasis, along with therapeutic perspectives of novel drugs that interfere with lectin–carbohydrate interactions.

Based on the information gathered on animal lectins in this book, a variety of medical and other applications are in the offing. Foremost among these is the lectin-replacement therapy for patients suffering from lectin deficiency defects. We have pointed out the advancements of

such studies where such progress has been made. Other uses in different stages of development are antibacterial drugs; multivalent hydrophobic carbohydrates for anti-adhesion therapy of microbial diseases; highly effective inhibitors of the selectins for treatment of leucocyte-mediated pathogenic conditions, such as asthma, septic shock, stroke, and myocardial infarction; inhibitors of the galectins and other lectins involved in metastasis; and application of lectins for facile and improved disease diagnosis. Recent advances in the discovery of M6PR-homologous protein family (Chap. 5), lectins of ERAD pathway, F-box proteins and M-type lectins (Chap. 6), and mannose receptor-targeted drugs and vaccines (Chaps. 8 and 46) can form the basis of cutting-edge technology in drug delivery devices.

Based on the structures of animal lectins, classified into at least 15 superfamilies, C-type lectins and galectins are the classical major families. Galectins are known to be associated with carcinogenesis and metastasis. Galectin-3 is a pleiotropic carbohydrate-binding protein, involved in a variety of normal and pathological biological processes. Its carbohydrate-binding properties constitute the basis for cell-cell and cell-matrix interactions (Chap. 12) and cancer progression (Chap. 13). Studies lead to the recognition of galectin-3 as a diagnostic/prognostic marker for specific cancer types, such as thyroid and prostate. In interfering with galectin-carbohydrate interactions during tumor progression, a current challenge is the design of specific galectin inhibitors for therapeutic purposes. Anti-galectin agents can restrict the levels of migration of several types of cancer cells and should, therefore, be used in association with cytotoxic drugs to combat metastatic cancer (Chap. 13). The properties of siglecs that make them attractive for cell-targeted therapies have been reviewed in Chaps. 16, 17, and 46.

F-type domains are found in proteins from a range of organisms from bacteria to vertebrates, but exhibit patchy distribution across different phylogenetic taxa, suggesting that F-type lectin genes have been selectively lost even between closely related lineages, thus making it difficult to trace the ancestry of the F-type domain. The F-type domain has clearly gained functional value in fish, whereas the fate of F-type domains in higher vertebrates is not clear, rather it has become defunct. Two genes encoding three-domain F-type proteins are predicted in the genome of the opossum (*Monodelphis domestica*), an early-branching mammal. There is plenty of scope to discover F-type lectins in mammalian vertebrates (Chap. 20). Since the reports on the C-reactive protein (CRP) as a cardiovascular marker (Chap. 8), novel biomarkers in cardiovascular and other inflammatory diseases have emerged in recent years. The substantial knowledge on CRP is now being complemented by new markers such as YKL-40, a member of chi-lectins group of CTLD (Chap. 19). The YKL-40 (chitinase-3-like protein 1, or human cartilage glycoprotein-39) displays a typical fold of family 18 glycosyl hydrolases and is expressed and secreted by several types of solid tumors, including glioblastoma, colon cancer, breast cancer, and malignant melanoma. Chitinase-3-like protein 1 was recently introduced into clinical practice; yet its application is still restricted.

In volume 2, we have mainly focused on C-type lectins, which have been extensively studied in vertebrates. A C-type lectin is a type of carbohydrate-binding protein domain that requires calcium for binding interactions in general. Drickamer et al. classified C-type lectins into seven subgroups (I to VII) based on the order of the various protein domains in each protein. This classification was subsequently updated in 2002, leading to seven additional groups (VIII to XIV). A further three subgroups (XV to XVII) were added recently. The C-type lectins share structural homology in their high-affinity carbohydrate recognition domains (CRDs) and constitute a large and diverse group of extracellular proteins that have been extensively studied. Their activities have been implicated as indispensable players in carbohydrate recognition, suggesting their possible application in discrimination of various correlative microbes and developing biochemical tools. The C-type lectins, structurally characterized by a double loop composed of two highly conserved disulfide bridges located at the bases of the loops, are believed to mediate pathogen recognition and play important roles in the innate immunity of both vertebrates and invertebrates. A large number of these proteins

have been characterized and more than 80 have been sequenced. Recent data on the primary sequences and 3D structures of C-type lectins have enabled us to analyze their molecular evolution. Statistical analysis of their cDNA sequences shows that C-type-lectin-like proteins, with some exceptions, have evolved in an accelerated manner to acquire their diverse functions.

The C-type lectin family includes the monocyte mannose receptor (MMR), mannose-binding lectin (MBL), lung surfactant proteins, ficolins, selectins, and others, which are active in immune functions and pathogen recognition (Chaps. 23–34 and 41–45). Several C-type lectins and lectin-like receptors have been characterized that are expressed abundantly on the surface of professional antigen-presenting cells (APCs). Dendritic cells (DCs) are equipped with varying sets of C-type lectin receptors that help them with the uptake of pathogens. Important examples are langerin, DC-SIGN, DC-SIGNR, DCAR, DCIR, dectins, DEC-205, and DLEC (Chaps. 34–36). DCs are key regulators in directing the immune responses and, therefore, are under extensive research for the induction of antitumor immunity. They scan their surroundings for recognition and uptake of pathogens. Intracellular routing of antigens through C-type lectins enhances loading and presentation of antigens through MHC class I and II, inducing antigen-specific CD4⁺ and CD8⁺ T-cell proliferation and skewing T-helper cells. These characteristics make C-type lectins interesting targets for DC-based immunotherapy. Extensive research has been performed on targeting specific tumor antigens to C-type lectins, using either antibodies or natural ligands such as glycan structures. In Chaps. 34–36, we have presented the current knowledge of DC receptors to exploit them for antitumor activity and drug targeting in the near future (Chap. 46).

The monocyte mannose receptor (MMR) or the mannose receptor (MR) (CD206) is a member of the Group VI C-type lectins along with ENDO180, DEC205, and the phospholipase A2 receptor. Expressed on a broad range of cell types, including tissue macrophages and various epithelial cells, the MMR is active in endocytosis and phagocytosis. It is also thought to be involved in innate immunity, though its exact role remains unclear. Structurally, MMR is a complex molecule, which has been reviewed as an R-type lectin in volume 1 (Chap. 15) and as a C-type lectin in volume 2 (Chap. 35). Further research is required to fully understand the function of MMR. In addition, the Reg family constitutes an interesting subset of the C-type lectin family. The Reg family members are small, secreted proteins, which have been implicated in a range of physiological processes such as acute phase reactants and survival/growth factors for insulin-producing pancreatic β -cells, neural cells, and epithelial cells of the digestive system (Chap. 39). The C-type lectin DC-SIGN is unique in the regulation of adhesion processes, such as DC trafficking and T-cell synapse formation, besides its well-studied function in antigen capture. In particular, the DC-SIGN and associated homologues contribute to the potency of DC to control immunity (Chaps. 36 and 46). There is always significant interest in the development of drug and antigen delivery systems via the oral route due to patient compliance and acceptability. The presence of DCs with knowledge of associated receptors in the gastrointestinal tract offers principles of methodology for the development of oral vaccines (Chap. 46).

The search of the database of NCBI revealed that the C-type lectins attract much more attention, which resulted in recent discoveries of novel groups of lectins (Groups XV–XVII; Chap. 40). The clinical applications of C-type lectins have been exemplified in Chaps. 42–46. Although a variety of lectins have enabled greater insight into the diversity and complexity of lectin repertoires in vertebrates in two volumes, the nature of the protein–carbohydrate interactions and the potential mechanisms of different functions for invertebrate lectins are under intense investigation. Future progress will elucidate the contribution of different lectin families and their cross talk with each other or with other molecules with respect to mounting protective immune responses in invertebrates and vertebrates.

MBL as a reconstitution therapy in genetically determined MBL deficiency has advanced significantly. Since the genetically determined MBL deficiency is very common and can be

associated with increased susceptibility to a variety of infections, the potential benefits of MBL reconstitution therapy still need to be evaluated. In a phase I trial on MBL-deficient healthy adult volunteers, MBL did not show adverse clinical effects (Chap. 23). SP-A and SP-D have been recently categorized as “Secretory Pathogen Recognition Receptors.” Treatment with a recombinant fragment of human SP-D consisting of a short collagen-like stalk (but not the entire collagen-like domain of native SP-D), neck, and CRD inhibited development of emphysema-like pathology in SP-D-deficient mice (Chaps. 24, 25, and 43). Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited nephropathy, affecting over 1:1000 of the population worldwide. It is a systemic condition with frequent hepatic and cardiovascular manifestations in addition to the progressive development of fluid-filled renal cysts that eventually result in loss of renal function in the majority of affected individuals. The cysts that grow in the kidneys of the majority of ADPKD patients are the result of mutations within the genes *PKD1* and *PKD2* that code for polycystin-1 (PC-1) and PC-2, respectively (Chap. 45). The annexins or lipocortins are a multigene family of proteins that bind to acidic phospholipids and biological membranes. Some of the annexins bind to glycosaminoglycans (GAGs) in a Ca^{2+} -dependent manner and function as recognition elements for GAGs in extracellular space. The emerging groups of C-type lectins include layilin, tetranectin, and chondrolectin (Group VIII of CTLD) (Chap. 40) and CTLD-containing protein - CBCP in Group XVII. Fras1, QBRICK/Frem1, Frem2, and Frem3 form the family of Group XVII (Chap. 41).

There is plenty of scope to discover lectins in invertebrates and amphibians which offer novel biomaterials useful in therapeutics, with a hope that the list of native lectins as well as genetically modified derivatives will grow with time. Thus, understanding animal lectins and the associated network of proteins is of high academic value for those working in the field of protein chemistry and designing new drugs on the principle of protein–carbohydrate or protein–protein interactions. Refined information on the sites of interactions on glycoproteins in toto with lectins is the subject of future study. Efforts are being made to develop an integrated knowledge-based animal lectins database together with appropriate analytical tools. Thus, *Animal Lectins: Form, Function, and Clinical Applications*, the Encyclopedia of Vertebrate Lectins, is unique in its scope and differs from earlier publications on animal lectins. It is more than lectinology and is suitable to the students and researchers working in the areas of biochemistry, glycobiology, biotechnology, biophysics, microbiology and immunology, pharmaceutical chemistry, biomedicine, and animal sciences in general.

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