

G. S. Gupta

Animal Lectins: Form, Function and Clinical Applications

Volume 1

G.S. Gupta

Animal Lectins: Form, Function and Clinical Applications

In Collaboration with Anita Gupta
and Rajesh K. Gupta

Principal author
G.S. Gupta, Ph. D.
Panjab University
Chandigarh 160014
India

ISBN 978-3-7091-1064-5 ISBN 978-3-7091-1065-2 (eBook)
DOI 10.1007/978-3-7091-1065-2
Springer Wien Heidelberg New York Dordrecht London

Library of Congress Control Number: 2012945422

© Springer-Verlag Wien 2012

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Contents of Volume 1

Part 1 Introduction

1 Lectins: An Overview	3
G.S. Gupta	
1.1 Lectins: Characteristics and Diversity	3
1.1.1 Characteristics	3
1.1.2 Lectins from Plants	4
1.1.3 Lectins in Microorganisms	5
1.1.4 Animal Lectins	5
1.2 The Animal Lectin Families	5
1.2.1 Structural Classification of Lectins	5
1.3 C-Type Lectins (CLEC)	8
1.3.1 Identification of CLEC	8
1.3.2 C-Type Lectin Like Domain (CTLD/CLRD)	8
1.3.3 Classification of CLRD-Containing Proteins	9
1.3.4 The CLRD Fold	9
1.4 Disulfide Bonds in Lectins and Secondary Structure	10
1.4.1 Disulfide Bond	10
1.4.2 Pathway for Disulfide Bond Formation in the ER of Eukaryotic Cells	10
1.4.3 Arrangement of Disulfide Bonds in CLRDs	10
1.4.4 Functional Role of Disulfides in CLRD of Vertebrates	11
1.4.5 Disulfide Bonds in Ca ²⁺ -Independent Lectins	12
1.5 Functions of Lectins	12
1.5.1 Lectins in Immune System	13
1.5.2 Lectins in Nervous Tissue	15
1.6 The Sugar Code and the Lectins as Receptors in System Biology	15
1.6.1 Host-Pathogen Interactions	16
1.6.2 Altered Glycosylation in Cancer Cells	17
1.6.3 Protein-Carbohydrate Interactions in Immune System	18
1.6.4 Glycosylation and the Immune System	19
1.6.5 Principles of Protein-Glycan Interactions	19
1.7 Applications of Lectin Research and Future Perspectives	21
1.7.1 Mannose Receptor-Targeted Vaccines	21
References	22

Part II Intracellular Lectins

2 Lectins in Quality Control: Calnexin and Calreticulin	29
G.S. Gupta	
2.1 Chaperons	29
2.1.1 Calnexin	30
2.1.2 Calnexin Structure	30
2.1.3 Calnexin Binds High-Mannose-Type Oligosaccharides	31
2.1.4 Functions of Calnexin	32
2.1.5 Patho-Physiology of Calnexin Deficiency	35
2.2 Calreticulin	36
2.2.1 General Features	36
2.2.2 The Protein	37
2.2.3 Cellular Localization of Calreticulin	40
2.2.4 Functions of Calreticulin	41
2.2.5 Structure-Function Relationships in Calnexin and Calreticulin	48
2.2.6 Pathophysiological Implications of Calreticulin	48
2.2.7 Similarities and Differences Between Cnx and Crt	50
2.2.8 Calreticulin in Invertebrates	51
References	52
3 P-Type Lectins: Cation-Dependent Mannose-6-Phosphate Receptor	57
G.S. Gupta	
3.1 The Biosynthetic/Secretory/Endosomal Pathways	57
3.1.1 Organization of Secretory Pathway	57
3.2 P-Type Lectin Family: The Mannose 6-Phosphate Receptors	62
3.2.1 Fibroblasts MPRs	63
3.2.2 MPRs in Liver	63
3.2.3 MPRs in CNS	63
3.2.4 CI-MPR in Bone Cells	64
3.2.5 Thyroid Follicle Cells	64
3.2.6 Testis and Sperm	64
3.2.7 MPRs During Embryogenesis	65
3.3 Cation-Dependent Mannose 6-Phosphate Receptor	65
3.3.1 CD-MPR- An Overview	65
3.3.2 Human CD-MPR	66
3.3.3 Mouse CD-MPR	66
3.4 Structural Insights	67
3.4.1 N-Glycosylation Sites in CD-MPR	67
3.4.2 3-D Structure of CD-MPR	67
3.4.3 Carbohydrate Binding Sites in MPRs	70
3.4.4 Similarities and Dis-similarities between two MPRs	70
3.5 Functional Mechanisms	71
3.5.1 Sorting of Cargo at TGN	71
3.5.2 TGN Exit Signal Uncovering Enzyme	72
3.5.3 Association of Clathrin-Coated Vesicles with Adaptor Proteins	72
3.5.4 Role of Di-leucine-based Motifs in Cytoplasmic Domains	73
3.5.5 Sorting Signals in Endosomes	74
3.5.6 Palmitoylation of CD-MPR is Required for Correct Trafficking	74
References	75

4 P-Type Lectins: Cation-Independent Mannose-6-Phosphate Receptors	81
G.S. Gupta	
4.1 Cation-Independent Mannose 6-Phosphate Receptor (CD222)	81
4.1.1 Glycoprotein Receptors for Insulin and Insulin-like Growth Factors	81
4.2 Characterization of CI-MPR/IGF2R	81
4.2.1 Primary Structures of Human CI-MPR and IGF2R Are Identical . . .	81
4.2.2 Mouse IGF2R/CI-MPR Gene	82
4.2.3 Bovine CI-MPR	82
4.2.4 CI-MPR in Other Species	83
4.3 Structure of CI-MPR	84
4.3.1 Domain Characteristics of IGF2R/CI-MPR (M6P/IGF2R)	84
4.3.2 Crystal Structure	85
4.4 Ligands of IGF2R/CI-MPR	86
4.4.1 Extracellular Ligands of IGF2R/CI-MPR	86
4.4.2 Binding Site for M6P in CI-MPR	86
4.4.3 The Non-M6P-Containing Class of Ligands	89
4.5 Complementary Functions of Two MPRS	90
4.5.1 Why Two MPRs	91
4.5.2 Cell Signaling Pathways	92
4.6 Functions of CI-MPR	92
4.7 Proteins Associated with Trafficking of CI-MPR	94
4.7.1 Adaptor Protein Complexes	94
4.7.2 Mammalian TGN Golgins	95
4.7.3 TIP47: A Cargo Selection Device for MPR Trafficking	95
4.7.4 Sorting Signals in GGA and MPRs at TGN	95
4.8 Retrieval of CI-MPR from Endosome-TO-GOLGI	97
4.8.1 Endosome-to-Golgi Retrieval of CIMPR Requires Retromer Complex	97
4.8.2 Retromer Complex and Sorting Nexins (SNX)	98
4.8.3 Small GTPases in Lysosome Biogenesis and Transport	100
4.8.4 Role for Dynamin in Late Endosome Dynamics and Trafficking of CI-MPR	100
4.9 CI-MPR/IGF2R System and Pathology	100
4.9.1 Deficiency of IGF2R/CI-MPR Induces Myocardial Hypertrophy . . .	100
4.9.2 MPRs in Neuromuscular Diseases	101
4.9.3 CI-MPR in Fanconi syndrome	101
4.9.4 Tumor Suppressive Effect of CI-MPR/IGF2R	101
References	102
5 Mannose-6-Phosphate Receptor Homologous Protein Family	109
G.S. Gupta	
5.1 Recognition of High-Mannose Type N-Glycans in ERAD Pathways	109
5.2 Proteins Containing M6PRH Domains	110
5.3 GlcNAc-Phosphotransferase	110
5.4 α -Glucosidase II	112
5.4.1 Function of α -Glucosidase II	112
5.4.2 M6PRH Domain in GII β	113
5.4.3 Two Distinct Domains of β -Subunit of GII Interact with α -Subunit	113
5.4.4 Polycystic Liver Disease (PCLD) and β -Subunit of Glucosidase II	114

5.5	Osteosarcomas-9 (OS-9)	115
5.5.1	The Protein	115
5.5.2	Requirement of HRD1, SEL1L, and OS-9/XTP3-B for Disposal of ERAD-Substrates	115
5.5.3	OS-9 Recognizes Mannose-Trimmed N-Glycans	116
5.5.4	Dual Task for Xbp1-Responsive OS-9 Variants	116
5.5.5	Interactions of OS-9	116
5.6	YOS9 from <i>S. cerevisiae</i>	118
5.7	Erlectin/XTP3-B	119
5.8	<i>Drosophila</i> Lysosomal Enzyme Receptor Protein (LERP)	119
5.9	MRL1	119
	References	120
6	Lectins of ERAD Pathway: F-Box Proteins and M-Type Lectins	123
	G.S. Gupta	
6.1	Intracellular Functions of N-Linked Glycans in Quality Control	123
6.2	The Degradation Pathway for Misfolded Glycoproteins	124
6.2.1	Endoplasmic Reticulum-Associated Degradation (ERAD)	124
6.2.2	Ubiquitin-Mediated Proteolysis	124
6.2.3	SCF Complex	125
6.2.4	F-Box Proteins: Recognition of Target Proteins by Protein-Protein Interactions	126
6.3	F-Box Proteins with a C-Terminal Sugar-Binding Domain (SBD)	127
6.3.1	Diversity in SCF Complex due to Lectin Activity of F-Box Proteins	127
6.3.2	Fbs Family	128
6.3.3	Fbs1 Equivalent Proteins	131
6.3.4	Ligands for F-Box Proteins	133
6.3.5	Evolution of F-Box Proteins	134
6.3.6	Localization of F-Box Proteins	134
6.3.7	Regulation of F-Box Proteins	134
6.4	α -Mannosidases and M-Type Lectins	135
6.4.1	α -Mannosidases	135
6.4.2	ER-associated Degradation-enhancing α -Mannosidase-like Proteins (EDEM)s	135
6.4.3	Functions of M-Type Lectins in ERAD	136
6.5	Derlin-1, -2 and -3	138
	References	139

Part III L-Type Lectins

7	L-Type Lectins in ER-Golgi Intermediate Compartment	145
	G.S. Gupta	
7.1	L-Type Lectins	145
7.1.1	Lectins from Leguminous Plants	145
7.1.2	L-Type Lectins in Animals and Other Species	145
7.2	ER-Golgi Intermediate Compartment	146
7.3	Lectins of Secretory Pathway	146
7.4	ER-Golgi Intermediate Compartment Marker-53 (ERGIC-53) or LMAN1	147
7.4.1	ERGIC-53 Is Mannose-Selective Human Homologue of Leguminous Lectins	147
7.4.2	Cells of Monocytic Lineage Express MR60: A Homologue of ERGIC-53	148

7.4.3	Rat Homologue of ERGIC53/MR60	149
7.4.4	Structure-Function Relations	150
7.4.5	Functions of ERGIC-53	152
7.4.6	Mutations in ERGIC-53 <i>LMAN1</i> Gene and Deficiency of Coagulation Factors V and VIII lead to bleeding disorder	154
7.5	Vesicular Integral Membrane Protein (VIP36) OR LMAN2	156
7.5.1	The Protein	156
7.5.2	VIP36-SP-FP as Cargo Receptor	157
7.5.3	Structure for Recognition of High Mannose Type Glycoproteins by VIP36	157
7.5.4	Emp47p of <i>S. cerevisiae</i> : A Homologue to VIP36 and ERGIC-53	158
7.6	VIP36-Like (VIPL) L-Type Lectin	158
	References	159
8	Pentraxins: The L-Type Lectins and the C-Reactive Protein as a Cardiovascular Risk	163
	G.S. Gupta	
8.1	Pentraxins and Related Proteins	163
8.2	Short Pentraxins	163
8.3	C-Reactive Protein	164
8.3.1	General	164
8.3.2	CRP Protein	164
8.3.3	Structure of CRP	165
8.3.4	Functions of CRP	166
8.4	CRP: A Marker for Cardiovascular Risk	168
8.4.1	CRP: A Marker for Inflammation and Infection	168
8.4.2	CRP: A Marker for Cardiovascular Risk	169
8.4.3	Role of Modified/Monomeric CRP	170
8.5	Extra-Hepatic Sources of CRP	171
8.6	Serum Amyloid P Component	171
8.6.1	Genes Encoding SAP	171
8.6.2	Characterization of SAP	172
8.6.3	Interactions of SAP and CRP	173
8.6.4	Functions of SAP	174
8.6.5	SAP in Human Diseases	175
8.6.6	SAP from <i>Limulus Polyphemus</i>	176
8.7	Female Protein (FP) in Syrian Hamster	176
8.7.1	Similarity of Female Protein to CRP and APC	176
8.7.2	Structure of Female Protein	177
8.7.3	Gene Structure and Expression of FP	177
8.8	Long Pentraxins	178
8.8.1	Long Pentraxins 1, -2, -3	178
8.9	Neuronal Pentraxins (Pentraxin-1 and -2)	178
8.9.1	Functions of Pentraxin 1 and -2	178
8.10	Pentraxin 3 (PTX3)	179
8.10.1	Characterization of PTX3	179
8.10.2	Cellular Sources of PTX3	180
8.10.3	Ligands	180
8.10.4	Regulation of PTX3	181
8.10.5	Functions of PTX3	182
	References	183

Part IV Animal Galectins

9 Overview of Animal Galectins: Proto-Type Subfamily	191
Anita Gupta and G.S. Gupta	
9.1 Galectins	191
9.2 Galectin Sub-Families	191
9.3 Galectin Ligands	192
9.4 Functions of Galectins	192
9.4.1 Functional Overlap/Divergence Among Galectins	193
9.4.2 Cell Homeostasis by Galectins	193
9.4.3 Immunological Functions	195
9.4.4 Signal Transduction by Galectins	196
9.4.5 Common Structural Features in Galectins	197
9.4.6 Galectin Subtypes in Tissue Distribution	198
9.5 Prototype Galectins (Mono-CRD Type)	199
9.5.1 Galectin-1	199
9.5.2 Galectin-2	199
9.5.3 Galectin-5	202
9.5.4 Galectin-7	202
9.5.5 Galectin-10 (Eosinophil Charcot-Leyden Crystal Protein)	203
9.5.6 Galectin-Related Inter-Fiber Protein (Grifin/Galectin-11)	204
9.5.7 Galectin-13 (Placental Protein -13)	205
9.5.8 Galectin 14	206
9.5.9 Galectin-15	206
9.6 Evolution of Galectins	207
9.6.1 Phylogenetic Analysis of Galectin Family	207
9.6.2 Galectins in Lower Vertebrates	207
References	208
10 Galectin-1: Forms and Functions	213
Anita Gupta	
10.1 The Subcellular Distribution	213
10.2 Molecular Characteristics	213
10.2.1 Galectin-1 Gene	213
10.2.2 X-Ray Structure of Human Gal-1	214
10.2.3 Gal-1 from Toad (<i>Bufo arenarum Hensel</i>) Ovary	216
10.2.4 GRIFIN Homologue in Zebrafish (DrGRIFIN)	216
10.3 Regulation of <i>Gal-1</i> Gene	216
10.3.1 Gal-1 in IMP1 Deficient Mice	216
10.3.2 Blimp-1 Induces Galectin-1 Expression	217
10.3.3 Regulation by Retinoic Acid	217
10.3.4 Regulation by TGF- β , IL-12 and FosB Gene Products	218
10.3.5 Regulation by Metabolites/Drugs/Other Agents	218
10.4 Gal-1 in Cell Signaling	220
10.5 Ligands/Receptors of Gal-1	220
10.5.1 Each Galectin Recognizes Different Glycan Structures	220
10.5.2 Interactions of Galectin-1	221
10.6 Functions of Galectin-1	223
10.6.1 Role of Galectin-1 in Apoptosis	223
10.6.2 Gal-1 in Cell Growth and Differentiation	225
10.6.3 Gal-1 and Ras in Cell Transformation	227
10.6.4 Development of Nerve Structure	228
10.6.5 Skeletal Muscle Development	232

10.6.6	Gal-1 and the Immune System	232
10.6.7	Role of Galectin-1 and Other Systems	235
	References	236
11	Tandem-Repeat Type Galectins	245
	Anita Gupta	
11.1	Galectin 4	245
11.1.1	Localization and Tissue Distribution	245
11.1.2	Galectin-4 Isoforms	246
11.1.3	Gal-4 from Rodents and Other Animals	247
11.1.4	Ligands for Galectin-4	248
11.1.5	Functions of Galectin-4	249
11.1.6	Galectin-4 in Cancer	251
11.2	Galectin-6	251
11.3	Galectin-8	251
11.3.1	Galectin-8 Characteristics	251
11.3.2	Functions of Galectin-8	253
11.3.3	Clinical Relevance of Gal-8	253
11.3.4	Isoforms of Galectin-8 in Cancer	253
11.4	Galectin-9	254
11.4.1	Characteristics	254
11.4.2	Stimulation of Galectin-9 Expression by IFN- γ	254
11.4.3	Crystal Structure of Galectin-9	255
11.4.4	Galectin-9 Recognizes <i>L. major</i> Poly- β -galactosyl Epitopes	255
11.4.5	Functions of Galectin-9	255
11.4.6	Galectin-9 in Clinical Disorders	257
11.4.7	Galectin-9 in Cancer	258
11.5	Galectin-12	259
	References	260
12	Galectin-3: Forms, Functions, and Clinical Manifestations	265
	Anita Gupta	
12.1	General Characteristics	265
12.1.1	Galectin-3 Structure	265
12.1.2	Galectin-3 Gene	266
12.1.3	Tissue and Cellular Distribution	266
12.2	Ligands for Galectin-3: Binding Interactions	268
12.2.1	Extracellular Matrix and Membrane Proteins	268
12.2.2	Intracellular Ligands	268
12.2.3	Carbohydrate Binding	269
12.2.4	Carbohydrate-Independent Binding	271
12.3	Functions	271
12.3.1	Galectin-3 is a Multifunctional Protein	271
12.3.2	Role in Cell Adhesion	272
12.3.3	Gal-3 at the Interface of Innate and Adaptive Immunity	272
12.3.4	Regulation of T-Cell Functions	274
12.3.5	Pro-apoptotic and Anti-apoptotic Effects	274
12.3.6	Role in Inflammation	276
12.3.7	Gal-3 in Wnt Signaling	278
12.3.8	In Urinary System of Adult Mice	278
12.3.9	Gal-3 in Reproductive Tissues	278
12.3.10	Gal-3 on Chondrocytes	278
12.3.11	Role of Gal-3 in Endothelial Cell Motility and Angiogenesis	279
12.3.12	Role in CNS	279

12.4	Clinical Manifestations of Gal-3	279
12.4.1	Advanced Glycation End Products (AGES)	279
12.4.2	GAL-3 and Protein Kinase C in Cholesteatoma	280
12.4.3	Gal-3 and Cardiac Dysfunction	280
12.4.4	Gal-3 and Obesity	281
12.4.5	Autoimmune Diseases	281
12.4.6	Myofibroblast Activation and Hepatic Fibrosis	282
12.5	Gal-3 as a Pattern Recognition Receptor	282
12.5.1	Gal-3 Binds to <i>Helicobacter pylori</i>	282
12.5.2	Recognition of <i>Candida albicans</i> by Macrophages Requires Gal-3	282
12.5.3	Gal-3 is Involved in Murine Intestinal Nematode and Schistosoma Infection	283
12.5.4	Up-Regulation of Gal-3 and Its Ligands by <i>Trypanosoma cruzi</i> Infection	283
12.6	Gal-3 as a Therapeutic Target	283
12.6.1	Gal-3: A Target for Anti-inflammatory/Anticancer Drugs	283
12.7	Xenopus-Cortical Granule Lectin: A Human Homolog of Gal-3	284
	References	284
13	Galectin-3: A Cancer Marker with Therapeutic Applications	291
	Anita Gupta	
13.1	Galectin-3: A Prognostic Marker of Cancer	291
13.2	Discriminating Malignant Tumors from Benign Nodules of Thyroid	291
13.2.1	Large-Needle Aspiration Biopsy	292
13.2.2	Fine-Needle Aspiration Biopsy	292
13.2.3	Combination of Markers	293
13.2.4	Hashimoto's Thyroiditis	294
13.3	Breast Cancer	294
13.4	Tumors of Nervous System	295
13.4.1	Galectins and Gliomas	295
13.5	Diffuse Large B-Cell Lymphoma	296
13.6	Gal-3 in Melanomas	297
13.7	Head and Neck Carcinoma	298
13.8	Lung Cancer	298
13.9	Colon Neoplastic Lesions	299
13.10	Expression of Gal-3 in Other Tumors	300
13.11	Gal-3 in Metastasis	302
13.12	β 1,6 N-acetylglucosaminyltransferase V in Carcinomas	302
13.13	Macrophage Binding Protein	303
13.14	Galectinomics	303
13.15	Mechanism of Malignant Progression by Galectin-3	304
13.16	Anti-Galectin Compounds as Anti-Cancer Drugs	305
	References	306
 Part V R-Type Animal Lectins		
14	R-Type Lectin Families	313
	Rajesh K. Gupta and G.S. Gupta	
14.1	Ricinus Communis Lectins	313
14.1.1	Properties of Ricin	313
14.1.2	Other R-Type Plant Lectins	314
14.2	R-Type Lectins in Animals	315
14.3	Mannose Receptor Family	315

14.4	UDP-Galnac: Polypeptide α -N-Acetyl-galactosaminyltransferases	316
14.4.1	Characteristics of UDP-GalNAc: α -N-Acetylgalactosaminyltransferases	316
14.4.2	The Crystal Structure of Murine ppGalNAc-T-T1	318
14.4.3	Parasite ppGalNAc-Ts	319
14.4.4	Crystal Structure of CEL-III from <i>Cucumaria echinata</i> Complexed with GalNAc	320
14.5	Microbial R-Type Lectins	321
14.5.1	<i>S. olivaceoviridis</i> E-86 Xylanase: Sugar Binding Structure	321
14.5.2	The Mosquitocidal Toxin (MTX) from <i>Bacillus sphaericus</i>	321
14.6	R-Type Lectins in Butterflies	322
14.6.1	Pierisin-1	322
14.6.2	Pierisin-2, Pierisin-3 and -4	324
14.7	Discoidin Domain and Carbohydrate-Binding Module	324
14.7.1	The Discoidin Domain	324
14.7.2	Discoidins from <i>Dictyostelium discoideum</i> (DD)	325
14.7.3	Discoidin Domain Receptors (DDR1 and DDR2)	326
14.7.4	Earth Worm (EW)29 Lectin	327
	References	327
15	Mannose Receptor Family: R-Type Lectins	331
	Rajesh K. Gupta and G.S. Gupta	
15.1	R-Type Lectins in Animals	331
15.2	Mannose Receptor Lectin Family	331
15.3	The Mannose Receptor (CD206)	332
15.3.1	Human Macrophage Mannose Receptor (MMR)	332
15.3.2	Structure-Function Relations	332
15.3.3	Cell and Tissue Distribution	334
15.3.4	Ligands	335
15.3.5	Functions of Mannose Receptor	336
15.3.6	Mouse Mannose Receptor	337
15.3.7	Interactions of MR with Branched Carbohydrates	339
15.3.8	Mannose Receptor-Targeted Drugs and Vaccines	339
15.4	Phospholipase A2-Receptors	339
15.4.1	The Muscle (M)-Type sPLA2 Receptors	340
15.4.2	Neuronal or N-Type PLA2 Receptor	342
15.5	DEC-205 (CD205)	342
15.5.1	Characterization	342
15.5.2	Functions of DEC-205	343
15.6	ENDO 180 (CD280)/uPARAP	343
15.6.1	Urokinase Receptor (uPAR)-Associated Protein	343
15.6.2	Interactions of Endo180	344
	References	345

Part VI I-Type Lectins

16	I-Type Lectins: Sialoadhesin Family	351
	G.S. Gupta	
16.1	Sialic Acids	351
16.2	Sialic Acid-Binding Ig-Like Lectins (I-Type Lectins)	352
16.2.1	Two Subsets of Siglecs	352
16.2.2	Siglecs as Inhibitory Receptors	353
16.2.3	Binding Characteristics of Siglecs	353
16.2.4	Siglecs of Sialoadhesin Family	354

16.3	Sialoadhesin (Sn)/Siglec-1 (CD169)	355
16.3.1	Characterization of Sialoadhesin/Siglec-1	355
16.3.2	Cellular Expression of Sialoadhesin	355
16.3.3	Ligands for Sialoadhesin	356
16.3.4	Sialoadhesin Structure	357
16.3.5	Regulation of Sialoadhesin	358
16.3.6	Functions of Sialoadhesin	358
16.3.7	Lessons from Animal Experiments	359
16.3.8	Interactions with Pathogens	360
16.4	CD22 (Siglec-2)	361
16.4.1	Characterization and Gene Organization	361
16.4.2	Functional Characteristics	361
16.4.3	Ligands of CD22	362
16.4.4	Regulation of CD22	364
16.4.5	Functions of CD22	365
16.4.6	Signaling Pathway of Human CD22 and Siglec-F in Murine	365
16.4.7	CD22 as Target for Therapy	367
16.5	Siglec-4 [Myelin-Associated Glycoprotein, (MAG)]	367
16.5.1	MAG and Myelin Formation	367
16.5.2	Characteristics of MAG	368
16.5.3	MAG Isoforms	368
16.5.4	Ligands of MAG: Glycan Specificity of MAG	369
16.5.5	Functions of MAG	370
16.5.6	MAG in Demyelinating Disorders	371
16.5.7	Inhibitors of Regeneration of Myelin	372
16.5.8	Axonal Regeneration by Overcoming Inhibitory Activity of MAG	372
16.5.9	Fish Siglec-4	373
16.6	Siglec-15	373
	References	373
17	CD33 (Siglec 3) and CD33-Related Siglecs	381
	G.S. Gupta	
17.1	Human CD33 (Siglec-3)	381
17.1.1	Human CD33 (Siglec-3): A Myeloid-specific Inhibitory Receptor	381
17.2	CD33-Related Siglecs (CD33-rSiglecs)	382
17.2.1	CD33-Related Siglecs Family	382
17.2.2	CD33-rSiglec Structures	382
17.2.3	Organization of CD33-rSiglec Genes on Chromosome 19q13.4	384
17.3	Siglec-5 (CD170)	384
17.3.1	Characterization	385
17.3.2	Siglec-5: An Inhibitory Receptor	385
17.3.3	Siglec-5-Mediated Sialoglycan Recognition	385
17.4	Siglec-6	386
17.4.1	Cloning and Gene Organization of Siglec-6 (OB-BP1)	386
17.4.2	Siglec-6 (OB-BP1) and Reproductive Functions	387
17.5	Siglec-7 (p75/AIRM1)	387
17.5.1	Characterization	387
17.5.2	Cytoplasmic Domain of Siglec-7 (p75/AIRM1)	387
17.5.3	Crystallographic Analysis	388
17.5.4	Interactions of Siglec-7	388
17.5.5	Functions of Siglec-7	389
17.6	Siglec-8	389
17.6.1	Characteristics and Cellular Specificity	389
17.6.2	Ligands for Siglec-8	390

17.6.3	Functions in Apoptosis	390
17.6.4	Siglec-8 in Alzheimer's Disease	391
17.7	Siglec-9	391
17.7.1	Characterization and Phylogenetic Analysis	391
17.7.2	Functions of Siglec-9	391
17.8	Siglec-10, -11, -12, and -16	392
17.8.1	Siglec-10	392
17.8.2	Siglec-11	392
17.8.3	Siglec-12	393
17.8.4	Siglec-16	394
17.9	Mouse Siglecs	394
17.9.1	Evolution of Mouse and Human CD33-rSiglec Gene Clusters	394
17.9.2	Mouse CD33/Siglec-3	394
17.9.3	Siglec-3-Related Siglecs in Mice	395
17.10	Glycoconjugate Binding Specificities of Siglecs	397
17.11	Functions of CD33-Related Siglecs	399
17.11.1	Endocytosis	399
17.11.2	Phagocytosis of Apoptotic Bodies	400
17.12	Siglecs as Targets for Immunotherapy	400
17.13	Molecular Diversity and Evolution of Siglec Family	401
	References	402

Part VII Novel Super-Families of Lectins

18	Fibrinogen Type Lectins	409
	Anita Gupta	
18.1	Ficolins	409
18.1.1	Ficolins versus Collectins	409
18.1.2	Characterization of Ficolins	409
18.1.3	Ligands of Ficolins	411
18.1.4	X-ray Structures of M, L- and H-Ficolins	412
18.1.5	Functions of Ficolins	413
18.1.6	Pathophysiology of Ficolins	415
18.2	Tachylectins	415
18.2.1	Horseshoe Crab Tachylectins	415
18.2.2	X-ray Structure	416
	References	417
19	Chi-Lectins: Forms, Functions and Clinical Applications	421
	Rajesh K. Gupta and G.S. Gupta	
19.1	Glycoside Hydrolase Family 18 Proteins in Mammals	421
19.1.1	Chitinases	421
19.2	Chitinase-Like Lectins: Chi-Lectins	421
19.3	YKL-40 [Chitinase 3-Like Protein 1 (CHI3L1)]	422
19.3.1	The Protein	422
19.3.2	Cell Distribution and Regulation	422
19.3.3	Ligands of YKL-40	423
19.3.4	The Crystal Structure of YKL-40	423
19.4	Human Cartilage 39-KDA Glycoprotein (or YKL-39)/(CHI3L2)	425
19.5	Ym1 and Ym2: Murine Proteins	426
19.5.1	The Protein	426
19.5.2	Crystal Structure of Ym1	427
19.5.3	Oviductin	427

19.6	Functions of CHI3L1 (YKL-40)	428
19.6.1	Role in Remodeling of Extracellular Matrix and Defense Mechanisms	428
19.6.2	Growth Stimulating Effect	428
19.7	Chi-Lectins As Markers of Pathogenesis	428
19.7.1	A Marker of Inflammation	428
19.7.2	CHI3L1 as Biomarker in Solid Tumors	431
19.7.3	Chitinase 3-Like-1 Protein (CHI3L1) or YKL-40 in Clinical Practice	432
19.8	Evolution of Mammalian Chitinases (-Like) of GH18 Family	433
	References	434
20	Novel Groups of Fuco-Lectins and Intelectins	439
	Rajesh K. Gupta and G.S. Gupta	
20.1	F-type Lectins (Fuco-Lectins)	439
20.1.1	F-type Lectins in Mammalian Vertebrates	439
20.2	F-type Lectins in Fish and Amphibians	440
20.2.1	<i>Anguilla Anguilla</i> Agglutinin (AAA)	440
20.2.2	FBP from European Seabass	442
20.2.3	Other F-type Lectins in Fish	442
20.2.4	F-Type Lectins in Amphibians	443
20.3	F-type Lectins in Invertebrates	444
20.3.1	Tachylectin-4	444
20.3.2	F-type Lectins from <i>Drosophila melanogaster</i>	445
20.3.3	F-Type Lectins in Sea Urchin	445
20.3.4	Bindin in Invertebrate Sperm	445
20.4	F-type Lectins in Plants	445
20.5	F-type Lectins in Bacteria	446
20.6	Fuco-Lectins in Fungi	447
20.6.1	Fuco-Lectin from <i>Aleuria Aurantia</i> (AAL)	447
20.7	Intelectins	448
20.7.1	Intelectin-1 (Endothelial Lectin HL-1/Lactoferrin Receptor or <i>Xenopus</i> Oocyte Lectin)	448
20.7.2	Intelectin-2 (HL-2) and Intelectin-3	449
20.7.3	Intelectins in Fish	450
20.7.4	Eglectin (XL35) or Frog Oocyte Cortical Granule Lectins	450
	References	451
21	Annexins (Lipocortins)	455
	G.S. Gupta	
21.1	Annexins	455
21.1.1	Characteristics of Annexins	455
21.1.2	Classification and Nomenclature	456
21.1.3	Annexins in Tissues	457
21.1.4	Functions of Annexins	458
21.2	Annexin Family Proteins and Lectin Activity	459
21.3	Annexin A2 (p36)	459
21.3.1	Annexin 2 Tetramer (A2t)	460
21.3.2	Crystal Analysis of Sugar-Annexin 2 Complex	461
21.3.3	Functions of Annexin A2	461
21.4	Annexin A4 (p33/41)	461
21.4.1	General Characteristics	461
21.4.2	Tissue Distribution	462
21.4.3	Characterization	463

21.4.4	Pathophysiology	463
21.4.5	Doublet p33/41 Protein	463
21.5	Annexin A5/Annexin V	464
21.5.1	Gene Encoding Human Annexin A5	464
21.5.2	Interactions of Annexin A5	464
21.5.3	Molecular Structure of Annexin A5	465
21.5.4	Annexin A5-Mediated Pathogenic Mechanisms	466
21.5.5	A Novel Assay for Apoptosis	466
21.5.6	Calcium-Induced Relocation of Annexins 4 and 5 in the Human Cells	467
21.6	Annexin A6 (Annexin VI)	467
21.6.1	Structure	467
21.6.2	Functions	467
	References	468