

Contents

Forewords V

Preface XXI

List of Contributors XXIII

Part One Chemical Basis

- 1 **The Biochemical Basis and Coding Capacity of the Sugar Code** 3
Harold Rüdiger and Hans-Joachim Gabius
 - 1.1 Etymological Roots 3
 - 1.2 What Projection Formulas Tell Us 4
 - 1.3 The Coding Capacity of the Sugar Code 8
 - 1.4 Conclusions 12
 - References 13
- 2 **Three-Dimensional Aspects of the Sugar Code** 15
Tibor Kožár, Sabine André, Jozef Uličný, and Hans-Joachim Gabius
 - 2.1 How to Obtain Information about Carbohydrate Conformation 15
 - 2.2 Complexity of Carbohydrate Flexibility 16
 - 2.3 How to Describe the Shape of Monosaccharides 17
 - 2.4 How to Describe the Shape of Di- and Oligosaccharides 18
 - 2.5 Additional Factors Influencing the Shape of Oligo- and Polysaccharides 22
 - 2.6 Examples of Di- and Oligosaccharide Conformations 23
 - 2.7 Carbohydrate-Protein Intermolecular Interactions and Reaction Mechanisms 26
 - 2.8 How to Perform Molecular Modeling of Large Glycans 28
 - 2.9 Conclusions 28
 - References 29

3	The Chemist's Way to Synthesize Glycosides	31
	<i>Stefan Oscarson</i>	
3.1	Synthesis of Oligosaccharides: Strategies	32
3.2	Glycosidic Bond Formation	33
3.3	Fischer Glycosylations	35
3.4	Glycosyl Donors	36
3.5	Anomeric Configuration: Stereoselectivity	38
3.5.1	Formation of 1,2- <i>Trans</i> -Linkages	39
3.5.2	Formation of 1,2- <i>Cis</i> -Linkages	40
3.6	Neuraminic Acid and Kdo-Glycoside Synthesis	42
3.7	Formation of Building Blocks: Orthogonal Glycosylations	44
3.8	Protecting Group Manipulations	46
3.9	An Example	46
3.10	Conclusions	49
	References	51
4	The Chemist's Way to Prepare Multivalency	53
	<i>Yoann M. Chabre and René Roy</i>	
4.1	Blocking Viral/Bacterial Adhesion	54
4.2	How to Prepare Multivalent Carbohydrates?	56
4.3	Neoglycoproteins	57
4.4	Neoglycolipids and Liposomes	58
4.5	Glycopolymers	60
4.6	Glycodendrimers	62
4.7	Glycodendrimer Syntheses	64
4.8	Conclusions	66
	References	69
5	Analytical Aspects: Analysis of Protein-Bound Glycans	71
	<i>Hiroaki Nakagawa</i>	
5.1	Detection of Glycans on Glycoproteins	71
5.2	Release of Glycans from Glycoproteins	73
5.3	Glycan Purification	74
5.4	Detailed Structural Analysis Using HPLC	76
5.5	Detailed Structural Analysis Using MS	78
5.6	Glycomic Analysis Using MS	78
5.7	Other Methods of Analysis	80
5.8	Glycopeptide Analysis Using MS	81
5.9	Conclusions	82
	References	82
	Part Two Natural Glycosylation—Glycoproteins	
6	N-Glycosylation	87
	<i>Christian Zuber and Jürgen Roth</i>	
6.1	NCAM1	87

6.2	Initial Steps in Asparagine-Linked Glycosylation	89
6.3	Trimming Reactions by α -Glucosidases and Interactions with ER Lectins	92
6.4	Quality Control of Protein Folding and Assembly: Machinery and Principal Mechanism	95
6.5	ER Exit—Facing a Crucial Decision and What Mannose Has to Do	96
6.6	How to Become a Mature N-Glycan?	99
6.6.1	Golgi Mannose Trimming as the Start for N-Glycan Elongation	100
6.6.2	Nucleotide Sugar Transporters Import the Fuel for Oligosaccharide Elongation	100
6.6.3	Glycosyltransferases: The Orderly Maturation Reactions	102
6.7	Structure Building by N-Acetylglucosaminyltransferase-I and Fucosyltransferase-VIII	103
6.8	Branching and Elongation Reactions	103
6.8.1	Mannosyl β -N-Acetylglucosaminyltransferases	103
6.8.2	N-Acetylglucosaminyl- β -Galactosyltransferases	104
6.8.3	Capping Sugars Provide Functions	104
6.8.4	Sialyltransferases	105
6.8.5	Fucosyltransferases	106
6.8.6	Glucuronyltransferases	106
6.8.7	Sulfotransferases	107
6.9	Diversity of N-Glycans: Structural and Functional Implications	107
6.10	Conclusions	109
	References	109
7	O-Glycosylation: Structural Diversity and Functions	111
	<i>Georgios Patsos and Anthony Corfield</i>	
7.1	Structure of O-Linked Glycans	111
7.2	Biosynthetic Routes for O-Glycans	121
7.3	Regulation of O-Glycosylation and Glycan Processing	125
7.3.1	O-GalNAc, Mucin Type	125
7.3.2	β -O-GlcNAc	127
7.3.3	O-Man	128
7.3.4	O-Fuc and O-Glc	128
7.4	Functions of O-Linked Glycosylation	129
7.4.1	O-GalNAc, Mucin Type	129
7.4.1.1	Protein Structure and Stability	129
7.4.1.2	Protein Conformation and Tertiary Structure	129
7.4.1.3	Protein Quaternary Structure and Molecular Association	130
7.4.1.4	Protein Stability: Protease and Heat Resistance	130
7.4.1.5	Recognition Phenomena	130
7.4.2	β -O-GlcNAc	130
7.4.2.1	Protein Structure and Stability	132
7.4.2.2	Recognition Phenomena and Disease	132
7.4.3	O-Man	132
7.4.3.1	Protein Structure and Stability	132

7.4.3.2	Recognition Phenomena	132
7.4.4	O-Fuc and O-Glc	132
7.4.4.1	Protein Structure and Stability	134
7.4.4.2	Recognition Phenomena	134
7.5	Mucins: A Major Group of O-Glycosylated Proteins	134
7.6	Conclusions	136
	References	137

8	Glycosylation of Model and 'Lower' Organisms	139
	<i>Iain B. H. Wilson, Katharina Paschinger, and Dubravko Rendić</i>	
8.1	Bacterial Glycosylation	139
8.2	Yeast Glycosylation	141
8.3	Plant Glycosylation	143
8.4	Insect Glycosylation	146
8.5	Worm Glycosylation	148
8.6	Protozoan Glycosylation	150
8.7	Fish Glycosylation	151
8.8	Conclusions	152
	References	153

9	Glycosylphosphatidylinositol Anchors: Structure, Biosynthesis and Functions	155
	<i>Hosam Shams-Eldin, Françoise Debierre-Grockiego, and Ralph T. Schwarz</i>	
9.1	Structure of GPI Anchors	155
9.1.1	Detection and Isolation of GPI-Anchored Proteins	158
9.1.2	Biosynthesis of GPI Anchors	160
9.2	Remodeling of Lipid Moieties of GPI Proteins	166
9.3	Chemical Synthesis of GPIs	167
9.3.1	Mutant Cells Lead the Way to Identification of Complementation Classes Involved in GPI Biosynthesis	167
9.3.2	Defects in GPI Anchor Biosynthesis	168
9.3.3	Function	169
9.4	Conclusions	171
	References	173

Part Three Natural Glycosylation—Glycolipids, Proteoglycans and Chitin

10	Glycolipids	177
	<i>Jürgen Kopitz</i>	
10.1	Classification and General Structures of Glycolipids	177
10.2	Glycoglycerolipids in Thylakoid Membranes	180
10.3	Glycolipids in Non-photosynthetic Bacteria	180
10.4	Bacterial Glycolipids in T-Cell Activation	182
10.5	Glycosphingolipids (GSLs)	183

10.6	Complex Neutral GSLs	183
10.7	Complex Acidic (Anionic) GSLs	185
10.8	Survey of GSL Functions	187
10.9	GSL Microdomains	188
10.10	GSLs as Attachment Sites for Viruses, Bacteria and Toxins	192
10.11	GSLs as Developmental or Differentiation Markers	193
10.12	Tumor-Associated GSL Antigens	193
10.13	Gangliosides in Neural Tissue	195
10.14	GSL Degradation and GSL Storage Disorders	195
10.15	Conclusions	196
	References	197
11	Proteoglycans	199
	<i>Eckhart Buddecke</i>	
11.1	Glycosaminoglycans: Components of Proteoglycans (PGs)	199
11.1.1	Structure	199
11.1.2	Biosynthesis	201
11.1.3	Catabolism	202
11.2	PGs	204
11.3	Large Aggregating (Hyaluronan-Binding) PGs	204
11.3.1	Aggrecan	205
11.3.2	Versican	206
11.3.3	Neurocan, Brevican	207
11.4	Small Leucine-Rich PGs	207
11.5	Basement Membrane PGs	209
11.6	Cell-Surface (Transmembrane) PGs	211
11.6.1	Syndecans	211
11.6.1.1	Structure	211
11.6.1.2	Functions	212
11.6.2	Glypicans	213
11.7	Conclusions	214
	References	215
12	Chitin	217
	<i>Hans Merzendorfer</i>	
12.1	Occurrence	218
12.2	Structure	219
12.3	Function	221
12.3.1	Fungal Cell Walls	222
12.3.2	Arthropod Cuticles and Shells	222
12.3.3	Peritrophic Matrices and Cocoons	223
12.3.4	Other Functions	224
12.4	Metabolism	224
12.5	Conclusions	228
	References	228

Part Four Protein–Carbohydrate Interactions

- 13 Protein–Carbohydrate Interactions: Basic Concepts and Methods for Analysis 233**
Dolores Solís, Antonio Romero, Margarita Menéndez, and Jesús Jiménez-Barbero
- 13.1 Atomic Features of Protein–Sugar Interactions 233
- 13.2 Role of Water in Protein–Sugar Interactions 237
- 13.3 Selection of Carbohydrate Conformers by Proteins 238
- 13.4 Thermodynamics of Protein–Carbohydrate Interactions 241
- 13.5 Conclusions 244
- References 245
- 14 How to Determine Specificity: From Lectin Profiling to Glycan Mapping and Arrays 247**
Hiroaki Tateno, Atsushi Kuno, and Jun Hirabayashi
- 14.1 Quantitative Aspects of Lectin Affinity 248
- 14.2 Frontal Affinity Chromatography (FAC) for Sugar–Protein Interactions 250
- 14.3 Automated FAC-FD System 252
- 14.4 From ‘Lectin Profiling’ to ‘Glycan Mapping’ 254
- 14.5 Lectin Microarray Enables Multiplexed Lectin–Glycan Interaction Analysis 254
- 14.6 Practice in Differential Glycan Profiling: Approaches and Applications 257
- 14.7 Conclusions 258
- References 259
- 15 The History of Lectinology 261**
Harold Rüdiger and Hans-Joachim Gabius
- 15.1 How Lectinology Started 261
- 15.2 Early Definitions 264
- 15.3 The Current Definition of the Term ‘Lectin’ 265
- 15.4 Recent Developments 266
- 15.5 Conclusions 267
- References 268
- 16 Ca^{2+} : Mastermind and Active Player for Lectin Activity (Including a Gallery of Lectin Folds) 269**
Hans-Joachim Gabius
- 16.1 Ca^{2+} : Organizing the Active Site 269
- 16.2 Ca^{2+} : Contacting Charged Ligands 272
- 16.3 Ca^{2+} : Neutralizing Negative Charges and Contacting Neutral Ligands 275
- 16.4 Conclusions 277
- References 278

17	Bacterial and Viral Lectins	279
	<i>Jan Holgersson, Anki Gustafsson, and Stefan Gaunitz</i>	
17.1	Bacterial Lectins	279
17.1.1	Fimbriae/Pili	282
17.1.1.1	Type 1 Fimbriae	283
17.1.1.2	Type P Fimbriae	283
17.1.1.3	Type S Fimbriae	284
17.1.1.4	Type IV Pili	284
17.1.2	Bacterial Surface Lectins	284
17.1.2.1	BabA and SabA	285
17.1.2.2	LecA and LecB	285
17.1.3	Toxins	285
17.1.3.1	Toxin A of <i>Clostridium difficile</i>	285
17.1.3.2	Cholera Toxin	286
17.1.3.3	Heat-Labile and Heat-Stable Toxins	286
17.1.3.4	Shiga and Shiga-Like Toxins	286
17.2	Virus Binding	287
17.2.1	Influenza Virus	290
17.2.1.1	Influenza Virus Surface Proteins	290
17.2.1.2	Epidemiology	290
17.2.1.3	Influenza Virus Species and Tissue Tropism	291
17.2.2	Rotavirus	291
17.2.3	Human Immunodeficiency Virus 1	292
17.2.4	Norovirus	292
17.2.5	Herpes viruses	293
17.2.6	Hepatitis C Virus	293
17.2.7	Paramyxoviridae	294
17.3	Carbohydrate-Based Antiinfectives	295
17.3.1	Neuraminidase Inhibitors as Drugs Against Influenza	295
17.3.2	Oligosaccharides as Inhibitors of Microbial Adhesion	295
17.3.3	A New Generation of Multivalent, Carbohydrate-Based Inhibitors of Microbial Adhesion	297
17.4	Conclusions	298
	References	299
18	Plant Lectins	301
	<i>Harold Rüdiger and Hans-Joachim Gabius</i>	
18.1	Nomenclature	301
18.2	Folding Patterns and Occurrence	305
18.3	Purification	309
18.4	Applications	311
18.5	Biological Functions	311
18.6	Conclusions	314
	References	315

19	Animal and Human Lectins	317
	<i>Hans-Joachim Gabius</i>	
19.1	Protein Folds with Lectin Activity	318
19.2	Functions of Animal and Human Lectins	320
19.3	Lectin Ligands and Affinity Regulation	326
19.4	Conclusions	327
	References	328
20	Routes in Lectin Evolution: Case Study on the C-Type Lectin-Like Domains	329
	<i>Jill E. Gready and Alex N. Zelensky</i>	
20.1	C-Type Lectin (CTL) Evolution as a Case Study	329
20.2	CTL Superfamily: Structures and Groups	330
20.3	Mechanism of Carbohydrate Binding	335
20.4	CTLs in the Genome Era	337
20.5	CTL Domain-Containing Proteins (CTLDcps) in Metazoans from Whole-Genome Analysis	339
20.6	Non-Metazoan CTLDs: From Viruses, Bacteria and Protozoa	343
20.7	CTLDcps in Genomes of Pre-Metazoans and Plants	344
20.8	Conclusions	344
	References	345
21	Carbohydrate–Carbohydrate Interactions	347
	<i>Iwona Bucior, Max M. Burger, and Xavier Fernández-Busquets</i>	
21.1	Molecular Basis of Carbohydrate–Carbohydrate Interactions	347
21.2	Carbohydrate–Carbohydrate Interactions in Cell Recognition	349
21.2.1	Proteoglycans	349
21.2.1.1	Carbohydrate Self-Interactions in Sponge Proteoglycans	349
21.2.1.2	Glycosaminoglycan Self-Interactions	351
21.2.2	Glycolipids	352
21.2.2.1	Le ^x –Le ^x Interactions	352
21.2.2.2	Gb4-Dependent Adhesion	352
21.2.2.3	GM3-Dependent Adhesion	353
21.3	Carbohydrates as DNA-Binding Motifs	354
21.4	New Strategies to Study Multivalent Carbohydrate–Carbohydrate Interactions	355
21.4.1	Analytical Ultracentrifugation	355
21.4.2	2D/3D Polyvalent Model Systems	356
21.4.2.1	Surface Plasmon Resonance (SPR)	356
21.4.2.2	Quartz Crystal Microbalance (QCM)	357
21.4.3	Single-Molecule Detection and Manipulation	358
21.4.3.1	Single-Molecule Force Spectroscopy (SMFS)	358
21.5	Conclusions	359
	References	361

Part Five Biomedical Aspects and Case Studies

22	Diseases of Glycosylation	365
	<i>Thierry Hennet</i>	
22.1	N-Glycosylation	366
22.2	O-Glycosylation	372
22.2.1	O-GalNAc Glycosylation	372
22.2.2	O-Man Glycosylation (O-Mannosylation)	374
22.2.3	O-Fuc Glycosylation (O-Fucosylation)	376
22.3	Glycosaminoglycans	377
22.4	Glycosphingolipids	379
22.5	Glycosylphosphatidylinositol Anchor	379
22.6	Defects Affecting Multiple Classes of Glycosylation	380
22.7	Trafficking Disorders	381
22.8	Conclusions	382
	References	383
23	Animal Models to Delineate Glycan Functionality	385
	<i>Koichi Honke and Naoyuki Taniguchi</i>	
23.1	Knockout Mouse	385
23.2	Specific Features of Glycogene KO	387
23.2.1	Relationship between Glycogenes and Related Glycans	387
23.2.2	Functional Association of Glycogenes	390
23.2.3	Which Are Essential—Glycans or Their Carriers?	392
23.2.4	Effects of Elimination of the Core and Terminal Structures of Glycans	393
23.2.5	Unexpected Findings Provide New Insights into Glycan Functions	398
23.2.6	Insights into Human Diseases	399
23.3	Other Gene Manipulation Techniques	400
23.4	Conclusions	401
	References	401
24	Glycobiology of Fertilization and Early Embryonic Development	403
	<i>Felix A. Habermann and Fred Sinowatz</i>	
24.1	Primer to Mammalian Fertilization	403
24.2	The Functional Morphology of the Zona Pellucida (ZP)	405
24.3	The Glycoproteins of the ZP and Their Encoding Genes	406
24.4	Glycan Structures of ZP Glycoproteins	407
24.5	The Synthesis of ZP Glycoproteins	409
24.6	Ligand Properties of ZP Glycans	410
24.7	The Glycoprotein Shell of Mammalian Embryos	413
24.8	Surface Glycans of Stem Cells	414
24.9	Conclusions	416
	References	416

25	Glycans as Functional Markers in Malignancy?	419
	<i>Sabine André, Jürgen Kopitz, Herbert Kaltner, Antonio Villalobo, and Hans-Joachim Gabius</i>	
25.1	The Past	420
25.2	The Present	421
25.3	The Future	430
25.4	Conclusions	430
	References	431
26	Small Is Beautiful: Mini-Lectins in Host Defense	433
	<i>Robert I. Lehrer</i>	
26.1	Meet the Families	433
26.2	Where Do α - and β -Defensins Reside?	435
26.3	Introducing θ -Defensins	436
26.4	Introducing Retrocyclins	437
26.5	Hemagglutination	438
26.6	How HIV-1 Enters Target Cells	440
26.7	Studies with Influenza A Virus	441
26.8	A Toxic Side-Trip	442
26.9	And Now, the Surprise	442
26.10	It Takes Two to Tangle	443
26.11	Which Human α - and θ -Defensins Are Lectins?	443
26.12	Conclusions	445
	References	445
27	Inflammation and Glycosciences	447
	<i>Reinhard Schwartz-Albiez</i>	
27.1	Sequence of Events	448
27.2	Where Do Carbohydrate-Lectin Interactions Play a Role During Acute Inflammation?	449
27.3	Selectins	451
27.4	Selectin Carbohydrate Ligands and Their Carrier Glycoproteins	451
27.5	Galectins	456
27.6	Siglecs	459
27.7	Other Lectins Involved in Antigen Recognition and Inflammatory Processes	462
27.8	Glycans Involved in Bacteria-Host Interactions	463
27.9	Glycosylation in Inflammatory Bowel Diseases	464
27.10	Conclusions	466
	References	466
28	Sugars as Pharmaceuticals	469
	<i>Helen M. I. Osborn and Andrea Turkson</i>	
28.1	Cancer Therapeutics	469
28.2	Viral Infections: HIV-1 and Influenza	473

28.3	Diabetes	476
28.4	Carbohydrate-Based Antibacterial Agents	477
28.5	Carbohydrate-Based Antithrombotic Agents	480
28.6	Conclusions	482
	References	482
29	Platelet Glycoproteins as Lectins in Hematology	485
	<i>Karin Hoffmeister and Hervé Falet</i>	
29.1	Platelet Physiology	485
29.2	GPIb-IX-V Complex	487
29.3	Cold-Induced Platelet Clearance	488
29.4	Long-Term Platelet Refrigeration May Reveal New Insights into Platelet Clearance	490
29.5	P-Selectin and PSGL-1	491
29.6	Conclusions	492
	References	493
30	Neurobiology Meets Glycosciences	495
	<i>Robert W. Ledeen and Gusheng Wu</i>	
30.1	Glucose and Glycogen as Energy Sources	497
30.2	Gangliosides as Primary Glycans of the Nervous System	497
30.3	Ganglioside Metabolism	499
30.4	Gangliosides of the Peripheral Nervous System	502
30.5	Ganglioside Functional Activities	503
30.6	Neural Glycoproteins: Overview	506
30.7	Neural Recognition Glycoproteins	507
30.8	Glycoproteins of the Synapse	510
30.9	Glycoproteins of Myelin	511
30.10	Proteoglycans and Extracellular Matrix of the Nervous System	512
30.11	Conclusions	514
	References	515
	Glossary	517
	Index	549