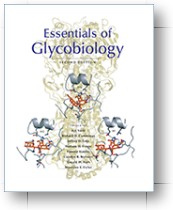
TABLE 1.2

“Universal” principles of glycobiology

Occurrence
All cells in nature are covered with a dense and complex array of sugar chains (glycans).
The cell walls of bacteria and archea are composed of several classes of glycans and glycoconjugates.
Most secreted proteins of eukaryotes carry large amounts of covalently attached glycans.
In eukaryotes, these cell-surface and secreted glycans are mostly assembled via the ER-Golgi pathway.
The extracellular matrix of eukaryotes is also rich in such secreted glycans.
Cytosolic and nuclear glycans are common in eukaryotes.
For topological, evolutionary, and biophysical reasons, there is little similarity between cell-surface/secreted and nuclear/cytosolic glycans.
Chemistry and structure
Glycosidic linkages can be in α- or β-linkage forms, which are biologically recognized as completely distinct.
Glycan chains can be linear or branched.
Glycans can be modified by a variety of different substituents, such as acetylation and sulfation.
Complete sequencing of glycans is feasible but usually requires combinatorial or iterative methods.
Modern methods allow in vitro chemoenzymatic synthesis of both simple and complex glycans.
Biosynthesis
The final products of the genome are posttranslationally modified proteins, with glycosylation being the most common and versatile of these modifications.
The primary units of glycans (monosaccharides) can be synthesized within a cell or salvaged from the environment.
Monosaccharides are activated into nucleotide sugars or lipid-linked sugars before they are used as donors for glycan synthesis.
Whereas lipid-linked sugar donors can be flipped across membranes, nucleotide sugars must be transported into the lumen of the ER-Golgi pathway.
Each linkage unit of a glycan or glycoconjugate is assembled by one or more unique glycosyltransferases.
Many glycosyltransferases are members of multigene families with related functions.
Most glycosyltransferases recognize only the underlying glycan of their acceptor, but some are protein or lipid specific.
Many biosynthetic enzymes (glycosyltransferases, glycosidases, sulfotransferases, etc.) are expressed in a tissue-specific, temporally regulated manner.
Diversity
Monosaccharides generate much greater combinatorial diversity than nucleotides or amino acids.
Further diversity arises from covalent modifications of glycans.
Glycosylation introduces a marked diversity in proteins.
Only a limited subset of the potential diversity is found in a given organism or cell type.
Intrinsic diversity (microheterogeniety) of glycoprotein glycans within a cell type or even a single glycosylation site.
The total expressed glycan repertoire (glycome) of a given cell type or organism is thus much more complex than the genome or proteome.
The glycome of a given cell type or organism is also dynamic, changing in response to intrinsic and extrinsic signals.
Glycome differences in cell type, space, and time generate biological diversity and can help to explain why only a limited number of genes are expressed from the typical genome.
Recognition
Glycans are recognized by specific glycan-binding proteins that are intrinsic to an organism.
Glycans are also recognized by many extrinsic glycan-binding proteins of pathogens and symbionts.

Glycan-binding proteins fall in two general categories: those that can usually be grouped by shared evolutionary origins and/or similarity in structural folds (lectins) and those that emerged by convergent evolution from different ancestors (e.g., GAG-binding proteins).
Lectins often show a high degree of specificity for binding to specific glycan structures, but they typically have relatively low affinities for single-site binding.
Thus, biologically relevant lectin recognition often requires multivalency of both the glycan and glycan-binding protein, to generate high avidity of binding.
Genetics
Naturally occurring genetic defects in glycans seem to be relatively rare in intact organisms. However, this apparent rarity may be due to a failure of detection, caused by unpredictable or pleiotropic phenotypes.
Genetic defects in cell-surface/secreted glycans are easily obtained in cultured cells but have somewhat limited biological consequences.
The same mutations typically have major phenotypic consequences in intact multicellular organisms.
Thus, many of the major roles of glycans likely involve cell–cell or extracellular interactions.
Nuclear/cytosolic glycans may have more cell-intrinsic roles, e.g., in signaling.
Complete elimination of major glycan classes generally causes early developmental lethality.
Organisms bearing tissue-specific alteration of glycans often survive, but they exhibit both cell-autonomous and distal biological effects.
Biological roles
Biological roles for glycans span the spectrum from nonessential activities to those that are crucial for the development, function, and survival of an organism.
Many theories regarding the biological roles of glycans appear to be correct, but exceptions occur.
Glycans can have different roles in different tissues or at different times in development.
Terminal sequences, unusual glycans, and modifications are more likely to mediate specific biological roles.
However, terminal sequences, unusual glycans, or modifications may also reflect evolutionary interactions with microorganisms and other noxious agents.
Thus, a priori prediction of the functions of a specific glycan or its relative importance to the organism is difficult.
Evolution
Relatively little is known about glycan evolution.
Interspecies and intraspecies variations in glycan structure are relatively common, suggesting rapid evolution.
The dominant mechanism for such evolution is likely the ongoing selection pressure by pathogens that recognize glycans.
However, glycan evolution must also preserve and/or elaborate critical intrinsic functions.
Interplay between pathogen selection pressure and preservation of intrinsic roles could result in the formation of “junk” glycans.
Such “junk” glycans could be the substrate from which new intrinsic functions arise during evolution.

From: Chapter 1, Historical Background and Overview



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Varki A, Cummings RD, Esko JD, et al., editors.
Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2009.

TABLE 1.1

Important discoveries in the history of glycobiology

Year(s)	Primary scientist(s)	Discoveries	Relevant chapters[a]
1876	J.L.W. Thudichum	glycosphingolipids (cerebrosides), sphingomyelin and sphingosine	10
1888	H. Stillmark	lectins as hemagglutinins	26, 28
1891	H.E. Fischer	stereoisomeric structure of glucose and other monosaccharides	2
1900	K. Landsteiner	human ABO blood groups as transfusion barriers	5, 13
1909	P.A. Levene	structure of ribose in RNA	1
1916	J. MacLean	isolation of heparin as an anticoagulant	16
1925	P.A. Levene	characterization of chondroitin sulfate and “mucoitin sulfate” (later, hyaluronan)	15, 16
1929	P.A. Levene	structure of 2-deoxyribose in DNA	1
1929	W.N. Haworth	pyranose and furanose ring structures of monosaccharides	2
1934	K. Meyer	hyaluronan and hyaluronidase	15
1934–1938	G. Blix, E. Klenk	sialic acids	14
1936	C.F. Cori, G.T. Cori	glucose-1-phosphate as an intermediate in glycogen biosynthesis	17
1942–1946	G.K. Hirst, F.M. Burnet	hemagglutination of influenza virus and “receptor-destroying enzyme”	14
1942	E. Klenk, G. Blix	gangliosides in brain	10, 14
1946	Z. Dische	colorimetric determination of deoxypentoses and other carbohydrates	2
1948–1950	E. Jorpes, S. Gardell	occurrence of N-sulfates in heparin and identification of heparan sulfate	16
1949	L.F. Leloir	nucleotide sugars and their role in the biosynthesis of glycans	4
1950	Karl Schmid	isolation of α1-acid glycoprotein (orosomucoid), a major serum glycoprotein	
1952	W.T. Morgan, W.M. Watkins	carbohydrate determinants of ABO blood group types	13
1952	E.A. Kabat	relationship of ABO to Lewis blood groups and secretor vs. nonsecretor status	13
1952	A. Gottschalk	sialic acid as the receptor for influenza virus	14
1952	T. Yamakawa	globoside, the major glycosphingolipid of the erythrocyte membrane	10
1956–1963	M.R.J. Salton, J.M. Ghuysen, R.W. Jeanloz, N. Sharon, H.M. Flowers	bacterial peptidoglycan backbone structure major structural polysaccharides in nature (chitin, cellulose, and peptidoglycan) are β1-4-linked throughout	20
1957	P.W. Robbins, F. Lipmann	biosynthesis and characterization of PAPS, the donor for glycan sulfation	4, 16
1957	H. Faillard, E. Klenk	crystallization of *N*-acetylneuraminic acid as product of influenza virus receptor-destroying enzyme (RDE) (“neuraminidase”)	14
1957–1963	J. Strominger, J.T. Park, H.R. Perkins, H.J. Rogers	mechanism of peptidoglycan biosynthesis and site of penicillin action	20
1958	H. Muir	“mucopolysaccharides” are covalently attached to proteins via serine	16

		via ceramide	
1960	D.C. Comb, S. Roseman	structure and enzymatic synthesis of CMP-*N*-acetylneuraminic acid	4, 14
1960–1965	O. Westphal, O. Lüderitz, H. Nikaido, P.W. Robbins	structure of lipopolysaccharides and endotoxin glycans	20
1960–1970	R. Jeanloz, K. Meyer, A. Dorfman	structural studies of glycosaminoglycans	15, 16
1961	S. Roseman, L. Warren	biosynthesis of sialic acid	4, 14
1961–1965	G.E. Palade	ER-Golgi pathway for glycoprotein biosynthesis and secretion	3
1962	A. Neuberger, R. Marshall, I. Yamashina, L.W. Cunningham	GlcNAc-Asn as the first defined carbohydrate-peptide linkage	8
1962	W.M. Watkins, W.Z. Hassid	enzymatic synthesis of lactose from UDP-galactose and glucose	4
1962	J.A. Cifonelli, J. Ludowieg, A. Dorfman	iduronic acid as a constituent of heparin	16
1962–1966	L. Roden, U. Lindahl	identification of tetrasaccharide linking glycosaminoglycans to protein core of proteoglycans	16
1962	E.H. Eylar, R.W. Jeanloz	demonstration of the presence of*N*-acetyllactosamine in α1-acid glycoprotein	13
1963	L. Svennerholm	analysis and nomenclature of gangliosides	10
1963	D. Hamerman, J. Sandson	covalent cross-linkage between hyaluronan and inter-α-trypsin inhibitor	15
1963–1964	B. Anderson, K. Meyer, V.P. Bhavanandan, A. Gottschalk	β-elimination of Ser/Thr-O-linked glycans	9
1963–1965	R. Kuhn, H. Wiegandt	structure of GM1 and other brain gangliosides	10
1963–1967	B.L. Horecker, P.W. Robbins, H. Nakaido, M.J. Osborn	lipid-linked intermediates in bacterial lipopolysaccharide and peptidoglycan biosynthesis	20
1964	V. Ginsburg	GDP-fucose and its biosynthesis from GDP-mannose	4
1964	B. Gesner, V. Ginsburg	glycans control the migration of leukocytes to target organs	26
1965	L.W. Cunningham	microheterogeneity of glycoprotein glycans	2, 8, 9
1965–1966	R.O. Brady	glucocerebrosidase is the enzyme deficient in Gaucher's disease	41
1965–1975	J.E. Silbert, U. Lindahl	cell-free biosynthesis of heparin and chondroitin sulfate	16
1965–1975	W. Pigman	tandem repeat amino acid sequences with Ser or Thr as O-glycosylation sites in mucins	9
1966	M. Neutra, C. Leblond	role of Golgi apparatus in protein glycosylation	3
1966–1969	B. Lindberg, S. Hakomori	refinement of methylation analysis for determination of glycan linkages	47
1966–1976	R. Schauer	multiple modifications of sialic acids in nature, their biosynthesis, and degradation	14
1967	L. Rodén, L.-Å. Fransson	semonstration of a copolymeric structure for dermatan sulfate	16
1967	R.D. Marshall	N-glycosylation occurs only at asparagine residues in the sequence motif Asn-X-Ser/Thr	8
1968	J.A. Cifonelli	description of the domain structure of heparan sulfate	16
1968	R.L. Hill, K. Brew	α-lactalbumin as a modifier of galactosyltransferase specificity	5
1969	L. Warren, M.C. Glick, P.W. Robbins	increased size of N-glycans in malignantly transformed cells	8, 44

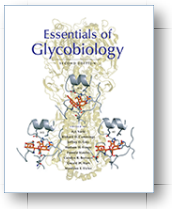
1969	R.J. Winzler	structures of O-glycans from erythrocyte membranes	9
1969–1974	V.C. Hascall, S.W. Sajdera, H. Muir, D. Heinegård, T. Hardingham	hyaluronan-proteoglycan interactions in cartilage	16, 17
1969	H. Tuppy, P. Meindl	synthesis of 2-deoxy-2,3-didehydro-Neu5Ac as viral sialidase inhibitor	14
1968–1970	E. Neufeld	identification of lysosomal enzyme deficiencies in the mucopolysaccharidoses	41
1969	G. Ashwell, A. Morell	glycans can control the lifetime of glycoproteins in blood circulation	26
1970	K.O. Lloyd, J. Porath, I.J. Goldstein	use of lectins for affinity purification of glycoproteins	45
1971–1973	L.F. Leloir	dolichylphosphosugars are intermediates in protein N-glycosylation	4, 8
1971–1975	P. Kraemer, J.E. Silbert	heparan sulfate as a common constituent of vertebrate cell surfaces	16
1971–1980	B. Toole	hyaluronan in differentiation, morphogenesis, and development	15
1972–1982	S. Hakomori	lacto- and globo-series glycosphingolipids as developmentally regulated and tumor-associated antigens	10, 44
1972	J.F.G. Vliegenthart	high-field proton NMR spectroscopy for structural analysis of glycans	2
1973	W.E. van Heyningen	glycosphingolipids are receptors for bacterial toxins	39
1973	J. Montreuil, R.G. Spiro, R. Kornfeld	a common pentasaccharide core structure of all N-glycans	8
1974	C.E. Ballou	structure of yeast mannans and generation of yeast mannan mutants	8, 46
1975	V.I. Teichberg	the first galectin	33
1975	V.T. Marchesi	primary structure of glycophorin, the first known transmembrane glycoprotein	3, 8, 9
1975–1980	A. Kobata	N- and O-glycan structural elucidation using multiple convergent techniques	2, 8, 9
1975–1980	P. Stanley, S. Kornfeld, R.C. Hughes	lectin-resistant cell lines with glycosylation defects	46
1977	W.J. Lennarz	Asn-X-Ser/Thr necessary and sufficient for lipid-mediated N-glycosylation	8
1977	I. Ofek, D. Mirelman, N. Sharon	cell-surface glycans as attachment sites for infectious bacteria	39
1977–1978	S. Kornfeld, P.W. Robbins	biosynthesis and processing of intermediates of N-glycans in protein glycosylation	8
1977	R.L. Hill, R. Barker	first purification of a glycosyltransferase involved in protein glycosylation	5, 8
1978	C. Svanborg	glycosphingolipids as receptors for bacterial adhesion	10, 39
1979–1982	E. Neufeld, S. Kornfeld, K. Von Figura, W. Sly	the mannose-6-phosphate pathway for lysosomal enzyme trafficking	30
1980–1983	F.A. Troy, J. Finne, S. Inoue, Y. Inoue	structure of polysialic acids in bacteria and vertebrates	14
1980	H. Schachter	role of glycosyltransferases in N- and O-glycan branching	5, 8
1980–1982	V.N. Reinhold, A. Dell, A.L. Burlingame	mass spectrometry for structural analysis of glycans	47, 48
1980–1985	S. Hakomori, Y. Nagai	glycosphingolipids as modulators of transmembrane signaling	10
1981–	M.J. Ferguson, I. Silman, M.	structural definition of glycosylphosphatidylinositol (GPI)	11

1985	Low	anchors	
1982	U. Lindahl, R.D. Rosenberg	specific sulfated heparin pentasaccharide sequence recognized by antithrombin	16, 35
1982	C. Hirschberg, R. Fleischer	transport of sugar nucleotides into the Golgi apparatus	3, 14
1984	G. Hart	intracellular protein glycosylation by O-GlcNAc	18
1984	J. Jaeken	description of “carbohydrate-deficient glycoprotein syndromes”	42
1985	M. Klagsbrun, D. Gospodarowicz	discovery of heparin–FGF interactions	35
1986	W.J. Whelan	glycogen is a glycoprotein synthesized on a glycogenin primer	17
1986	J.U. Baenziger	structures of sulfated N-glycans of pituitary hormones	13, 28
1986	Y. Inoue, S. Inoue	discovery of 2-keto-3-deoxynononic acid (Kdn) in rainbow trout eggs	14
1986	P.K. Qasba, J. Shaper, N. Shaper	cloning of first animal glycosyltransferase	5
1987	Y-C. Lee	high-performance anion-exchange chromatography of oligosaccharides with pulsed amperometric detection (HPAEC-PAD)	47

This time line of events is deliberately terminated about 20 years ago, on the assumption that it can take a long time to be certain that a particular discovery has had a major impact on the field. Historical details about several of these discoveries can be found in the “Classics” series of the *Journal of Biological Chemistry* (see http://www.jbc.org/, click on “Classic Articles,” and search by author name).

a Indicates main chapter(s) of this book in which the relevant topics are covered.

From: Chapter 1, Historical Background and Overview



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