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SPECIAL INVITED REVIEW

Biological roles of oligosaccharides: all of the theories are correct

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Many different theories have been advanced concerning the biological roles of the oligosaccharide units of individual classes of glycoconjugates. Analysis of the evidence indicates that while all of these theories are correct, exceptions to each can also be found. The biological roles of oligosaccharides appear to span the spectrum from those that are trivial, to those that are crucial for the development, growth, function or survival of an organism. Some general principles emerge. First, it is difficult to predict *a priori* the functions a given oligosaccharide on a given glycoconjugate might be mediating, or their relative importance to the organism. Second, the same oligosaccharide sequence may mediate different functions at different locations within the same organism, or at different times in its ontogeny or life cycle. Third, the more specific and crucial biological roles of oligosaccharides are often mediated by unusual oligosaccharide sequences, unusual presentations of common terminal sequences, or by further modifications of the sugars themselves. However, such oligosaccharide sequences are also more likely to be targets for recognition by pathogenic toxins and microorganisms. As such, they are subject to more intra- and inter-species variation because of ongoing host–pathogen interactions during evolution. In the final analysis, the only common features of the varied functions of oligosaccharides are that they either mediate 'specific recognition' events or that they provide 'modulation' of biological processes. In so doing, they generate much of the functional diversity required for the development and differentiation of complex organisms, and for their interactions with other organisms in the environment.

Key words: biological roles/glycoconjugates/oligosaccharides

Introduction

The ability to accurately sequence the oligosaccharide units of glycoconjugates has revealed a remarkable complexity and diversity of these molecules (1–18). However, despite some observations suggesting important biological roles for these sugar chains, a single common theory has not emerged to explain this diversity. As recently as 1988, it was stated that while '. . . the functions of DNA and proteins are generally known . . . it is much less clear what carbohydrates do' (12). A variety of theories have been advanced regarding the biological roles of the oligosaccharides, and have been presented in a number of monographs (1–18) and review articles (19–148). These include a purely structural role, an aid in the conformation and stability of proteins, the provision of target structures for microorganisms, toxins and antibodies, the masking of such target structures, control of the half-life of proteins and cells, the modulation of protein functions, and the provision of ligands for specific binding events mediating protein targeting, cell–matrix interactions or cell–cell interactions. Most of these discussions have focused either on one specific type of glycoconjugate (e.g. glycoprotein, proteoglycan or glycolipid) or on one specific theory of function. In this overview, an attempt is made to consider together all of these theories regarding all of the major types of glycoconjugates. Although the emphasis of this review is somewhat biased towards the glycoprotein oligosaccharides of higher animal cells, the principles that emerge appear to be generally applicable to glycoconjugates in all types of organisms.

Because of the broad and diverse nature of the subjects discussed here, a comprehensive bibliography has not been presented. In general, the original references are from the last 15 years, with a very limited representation of earlier citations. For detailed discussions of the classic and original literature on some of these matters, the interested reader is referred to the list of monographs (1–18) and reviews (19–148) provided.

The difficulty in predicting specific rules for oligosaccharide functions: *N*- and *O*-linked sugar chains as examples

Of all of the different types of glycosylation, the *N*-asparagine-linked sugar chains are the easiest to manipulate in experimental systems. Feasible approaches include the enzymatic or chemical removal of completed sugar chains, prevention of initial glycosylation, alteration of oligosaccharide processing, elimination of specific glycosylation sites, and the study of natural variants and genetic mutants in glycosylation. Such approaches have been used extensively to explore the biological roles of these sugar chains on a variety of glycoproteins (reviewed in 5, 8, 9, 12, 15–17, 20–36, 107–115, 126–131). A summary of many such studies is reported in Table I and a shorter list of similar experiments for *O*-linked oligosaccharides is presented in Table II. It can be seen that the consequences of altering these types of glycosylation range from being essentially undetectable, to the complete loss of particular functions, or even loss of the entire protein itself. Even within a given group of proteins (e.g. cell surface receptors or enzymes), the effects of altering glycosylation are highly variable and quite unpredictable. Furthermore, the same modification in glycosylation can have a dramatically opposite effect on *in vivo* function versus that observed for *in vitro* function (for example, see the studies on erythropoietin and the gonadotrophic hormones referred to in Table I). These facts underscore a basic principle about the biological roles of oligosaccharides: they appear to range from

Table I. Effects of altered *N*-linked oligosaccharides on the biosynthesis, transport and functions of glycoproteins

Protein	Effect of lack/alteration of oligosaccharides	Examples
Enzymes		
Most lysosomal enzymes[a,b,c,d]	Loss of targeting signal for delivery of enzymes to lysosomes	(107–111)
Lysosomal β-glucosidase[a]	Complete deglycosylation causes complete loss of activity	(149)
Lipoprotein lipase[c,d]	Core glycosylation required for secretion and activity. Processing of oligosaccharides not important for either	(150–152)
Yeast acid phosphatase[a,d]	Loss of activity and conformation. Increased susceptibility to denaturation and proteolysis	(153,154)
HMG-CoA reductase	>90% decrease in activity (direct or indirect effect?)	(155)
Lecithin:cholesterol acyltransferase[c]	Reduction in catalytic activity without change in K_m	(156)
Hepatic lipase[d]	Reduced secretion, normal catalytic activity	(157)
Arylsulphatase A[d]	Variable loss of mannose-6-phosphate-dependent trafficking	(158)
Yeast carboxypeptidase Y[d]	Reduced transport rate, especially at higher temperatures. No change in sorting, stability or activity	(159)
Propapain[d]	*N*-Glycosylation of Pro-region required for transport and secretion	(160)
α_1-Antitrypsin[d]	Altered CD spectrum and folding. Aggregation	(161)
Mucor renin expressed in yeast[d]	Decreased secretion and decreased activity	(162)
Purified lysosomal alpha-L-fucosidase[a]	No effect on activity or conformation. Shift of pH optimum, decreased stability in acid and heat	(163)
Ecto 5′-nucleotidase[b,c]	No change in subcellular distribution, or GPI-anchor formation	(164)
Pancreatic ribonuclease B[a,c]	Folding kinetics unchanged, increased susceptibility to proteases	(21,165-167)
UDP-glucuronosyltransferases[a]	No change in catalytic activity or substrate preference	(168)
Testicular hyaluronidase[a]	No change in enzymatic activity. Improved recognition by antibodies	(169)
Hormones/cytokines/growth factors		
Glycoprotein hormones (HCG, LH, TSH, prolactin)[a,b,c,d,e]	Complex effects. Altered combining of α- and β-subunits. In some cases, agonist converted into antagonist by loss of glycosylation. Altered glycosylation causes changes in specificity, affinity, and intracellular signalling *in vitro*. Effects on *in vivo* action are different, because of altered clearance	(126, 170–194)
Granulocyte/macrophage colony-stimulating factor (GM-CSF)[a,c,d]	Graded increase in receptor binding and activity with decreased glycosylation. However, increased antigenicity and rapid clearance of unglycosylated form	(195–198)
Erythropoietin[a,c,d,e]	Complex effects. Failure of secretion, decreased stability, and decreased biological activity if multiple glycosylation sites are eliminated. Desialylation and/or less branched oligosaccharides give increased activity *in vitro*, but decreased activity *in vivo*	(129,199–208)
IgE binding factors[d]	IgE potentiating factor converted into IgE suppressive factor?	(209–211)
Interleukin-4[a,e]	Increase in activity with decrease in glycosylation	(212)
Vascular endothelial growth factor[b]	Markedly decreased rate and efficiency of secretion. No loss of binding or of activity in increasing vascular permeability	(213, 214)
Yeast MFα1 precursor[d]	Delayed transit through the secretory pathway	(215)
Nerve growth factor[a]	Natural glycosylated variant still has biological activity	(216)
Scatter factor[a]	No change in secretion or activity	(217)
Interferon-gamma[a]	No change in antiviral activity or target cell specificity	(218)
Viral glycoproteins		
HIV virus glycoprotein (GP120)[a,b,c,d]	Prevention of glycosylation or prevention of glucose removal results in markedly lowered fusion activity and decreased infectivity	(219–227)
Some viral coat proteins[a,d,e]	Variable alterations in antigenicity; increased reactivity with polyclonal antisera upon removal of chains	(228–233)
Some (not all) viral coat proteins[b,c,d]	Complex and variable effects. Complete loss of glycosylation can result in misfolding, retention in the ER, proteolytic degradation and loss of virion production. Alteration of individual sites shows varying effects on cell surface expression. Alteration in late processing has little effect on expression or virion production.	(234–242)
Plasma proteins/coagulation factors		
Immunoglobulin D[a]	Removal causes loss of binding by IgD receptors	(243)
Immunoglobulins[a,b,c,d,e]	Complex effects. Altered secretion (variable). Alteration of several secondary effector functions of the Fc region. Agalactosyl IgG is associated with granulomatous diseases. Variable region glycosylation can enhance antigen binding	(34, 244–254)

Table I. *continued*

Protein	Effect of lack/alteration of oligosaccharides	Examples
Tissue-type plasminogen activator[a,d,e]	Increased enzymatic activity and/or lysine binding of certain glycoforms. Glycosylation alters conversion to two-chain form	(24, 255–261)
Haptoglobin[a]	Loss of ability to form a complex with haemoglobin	(262)
Antithrombin III_β—natural variant with decreased carbohydrate	Increased antithrombin activity. Enhanced heparin binding(?)	(263, 264)
Protein C[d] (different sites gave different effects)	No effect on gamma-carboxylation. Improved anticoagulant (increase in K_{cat}, decrease in K_m). Increase in rate of activation by thrombin/thrombomodulin complex (decrease in K_m)	(265)
Plasminogen[d,e]	Variations in glycosylation or sialylation associated with differences in cell-surface binding, circulatory half-time and fibrinolytic activity	(266–268)
β2-Glycoprotein[a]	Altered re-folding	(269)
Pro-urokinase[c]	Recombinant or mutated enzyme without glycosylation at Asn-302 is two-fold more efficient in activating plasmin	(270)
C1 inhibitor Ta[e]	Additional glycosylation site causes dysfunction and disease	(271)
Von Willebrand factor[a]	Variable effects on multimeric structure and altered function. Increased susceptibility to proteases	(272–275)
Fibrinogen[a,d,e]	Altered polymerization/aggregation. Sialic acids are low-affinity calcium-binding sites that can influence fibrin assembly	(276–280)
Galactoglycoprotein[a]	Enzymatic removal of ~96% of the carbohydrate caused large changes in CD spectra with increase in the magnitude of the molar ellipticity and amount of β-turns, and a reduction in random coils	(281)
Corticosteroid-binding globulin[b,e]	Acquisition of binding activity requires glycosylation	(282)
C5a (des-Arg form)[a,e]	Removal of oligosaccharide greatly enhances activity	(283)
Complement subcomponent Cs1[d]	No loss of ability to form the functional C1 complex	(284)
Amyloid peptide precursor[d]	Glycosylation improves trypsin inhibition by Kunitz-type domain	(285)
Thyroxine-binding globulin[a]	Decreased stability. Small change in affinity for thyroxine and immunoreactivity	(286, 287)
Androgen-binding protein[d]	Decreased secretion. No change in androgen binding	(288)
Folate-binding protein[b]	Initial glycosylation required for acquisition of binding function	(289)
Protein S (Heerlen polymorphism)[e]	Loss of glycosylation site causes no change in protein C binding	(290)
Matrix proteins		
Fibronectin[a,b]	Increased susceptibility to proteases	(21, 291)
Collagen IV 7S tetramerization domain	Modelling predicts that oligosaccharides are critical in assembly	(292)
Bone and platelet osteonectin[e]	Differences in glycosylation alter collagen-binding properties	(293)
Membrane proteins/receptors		
EGF receptor[b,c]	Glycosylation-dependent acquisition of ligand-binding capacity. Thereafter, oligosaccharides not required for binding	(115, 294)
Insulin and insulin-like growth factor-I receptors[c,d]	Loss of binding with complete deglycosylation only. Partial changes in binding affinity/specificity with altered glycosylation. Some studies show loss of tyrosine kinase activity	(295–299)
Basic fibroblast growth factor receptor[a]	Loss of binding of bFGF	(300)
Somatostatin receptor in rat brain and AtT-20 cells[a]	Sialic acids on the *N*-linked oligosaccharides are required for maintenance of the high-affinity binding state	(301)
Intercellular adhesion molecule I (ICAM-I)[d]	Glycosylation at a single site affects binding to Mac-1, but not to LFA-1	(302)
Fibronectin receptor ($\alpha_5\beta_1$ integrin)[c]	Normal biosynthesis and expression. Loss of ligand binding (?)	(303, 304)
Lymphocyte CD2[a,d]	Single glycosylation site required for binding of CD2 to CD58 on another cell. Postulated that glycosylation is required for stabilizing domain 1, which is involved in adhesion	(305)
C3b/C4b receptor[a,e]	Decreased surface expression, increased turnover. No change C3 binding	(306)
CR2/Epstein–Barr virus receptor[b]	Decreased surface expression. Increased turnover	(307)
MHC Class II molecules[d]	Variable loss of antigen-presenting function. No loss of peptide-binding function of purified protein	(308, 309)
Lutropin receptor[a,c]	Loss of surface expression. No change in ligand-binding capacity	(310)
Organic cation transporter of opossum kidney[b,c]	Increase in K_m without affecting V_{max} of transport	(311)
Glucose transporters[a,d]	Increase in *K*m for glucose. Partial or complete loss of activity	(312–314)
GM-CSF receptor[a,c]	Expression of α-chain abolished. β-chain expression normal	(315)
Erythrocyte band 3 protein[a]	Increased aggregation. No change in CD spectra, proteolytic susceptibility or anion transport activity	(316)
Erythrocyte CD59 complement inhibitor[a,c]	No change in ability to bind CD8/CD9. Loss (~90%) of inhibitory function	(317)
β-2 Adrenergic receptors[c,d]	No change in expression of ligand affinity. Uncoupling of adenylate cyclase	(318–320)
Thrombin receptor[b]	Partial loss of high-affinity binding	(321)
gp80 glycoprotein of MDCK cells[b]	Loss of apical polarized targeting	(322)
Transferrin receptor expressed in various cell types[d]	Decreased dimer expression. Decreased binding affinity in intact cells. Elimination of glycosylation sites causes partial ER retention and degradation	(323–326)

Table I. *continued*

Protein	Effect of lack/alteration of oligosaccharides	Examples
Nicotinic acetylcholine receptor[c]	Decreased expression (increased degradation?), no change in binding affinity	(327)
VIP receptor[a]	No change in expression. Decreased binding affinity	(328)
Membrane Class I MHC protein	Increased lateral mobility in the membrane	(329)
Vasopressin receptor of LLC-PK1 cells[b,c]	Inhibition of biosynthesis and internalization	(330)
Muscarinic acetylcholine receptor[d]	Decreased expression with some mutants. Small change in binding affinity. No change in turnover or functional response	(331)
Low-density lipoprotein receptor[b,c]	No change in expression or in recycling; ~50% decrease in ligand binding capacity. Redistribution between intracellular and surface locations	(332)
Interferon-gamma receptor[b,c]	Normal expression. Loss of ligand binding in the intact cell. However, the purified form is active	(333, 334)
Asialoglycoprotein receptor[a,b]	No change in expression, binding or turnover	(335)
46 kDa mannose-6-phosphate receptor[d]	Glycosylation required for stability of the high-affinity binding state, but not for binding itself, nor for intracellular stability	(336)
Nucleoside transporter(s) of L1210 cells[b]	No effect on synthesis or expression. Transport partially affected	(337)
CD4 protein[b,c,d]	Loss of one glycosylation site tolerated. Loss of both sites results in ER retention and degradation	(338, 339)
Thyrotrophin receptor[d]	Expression unchanged. Elimination of certain sites causes loss of binding	(340)
PDGF receptor[c]	Glycosylation not required for acquisition of ligand-binding capacity	(341)
Miscellaneous		
Jack bean concanavalin A[d,e]	*N*-Linked oligosaccharide keeps the precursor in an inactive form, until it is deglycosylated during later processing	(342, 343)
Cobra venom factor[a]	Complete deglycosylation abolishes complement activation	(344)
Gastric mucin[b]	Loss of covalent oligomerization	(345)
Lactotransferrin[a]	Loss of iron-binding activity	(346)
Rat intrinsic factor[c]	Normal secretion and cobalamin binding. Increased sensitivity to proteases (important for normal function in the gut)	(347)
Thyroglobulin[a,b]	Altered iodotyrosine-iodotyrosine interactions and immunoreactivity	(348, 349)
Spinach chloroplast coupling factor[a]	ATPase activity intact. Photophosphorylation activity lost	(350)
Many secreted animal proteins[c]	Prevention of glucose removal slows secretion, while blocking of late processing accelerates secretion in many glycoproteins	(351–355)
Plant glycoproteins secreted by sycamore cells in culture[b]	Prevention of glycosylation causes marked decrease in secretion, whereas altered processing has little effect	(356)

Note: unless otherwise stated, the proteins are of mammalian origin.
[a]Enzymatic or chemical removal of *N*-linked oligosaccharides.
[b]Prevention of *N*-linked glycosylation by tunicamycin (can have pleiotropic effects on other proteins in the same cell).
[c]*N*-Linked glycosylation processing inhibitor(s) (can have pleiotropic effects on other proteins in the same cell).
[d]Genetically engineered change in glycosylation.
[e]Natural genetic variant or defect.

trivial to crucial, depending on the glycoconjugate, the oligosaccharide structure, the biological context and the question being asked.

Can one make any sense out of these diverse and confusing findings? Most prior attempts to approach this issue have focused on either a single type of glycosylation or on a single theory of their function. In the following pages, an attempt is made to undertake a global overview of most of the known facts concerning the biological roles of oligosaccharides of major classes of glycoconjugates in eukaryotic cells, and to synthesize some general principles for understanding them. Much of the actual data is presented in table form and is necessarily simplified and/or incomplete. For more details, the interested reader is referred to the original literature cited in these tables, and to the monographs and reviews mentioned earlier.

'Structural', 'protective' and 'stabilizing' roles of oligosaccharides

There is little doubt that some oligosaccharides, such as those of the proteoglycans and the collagens, are important in the physical maintenance of tissue structure, integrity and porosity (see Table III). It is also clear that the 'coating' of oligosaccharides on many glycoproteins can serve to protect the polypeptide chain from recognition by proteases or antibodies (see Tables I, II and III) and that the coating of glycoconjugates covering a whole cell can present a 'glycocalyx' of substantial proportions. Another well-accepted function of the oligosaccharide units of glycoproteins is that they are involved in the initiation of correct polypeptide folding in the rough endoplasmic reticulum (ER), and in the subsequent maintenance of protein solubility and conformation (see examples in Tables I and II). Thus, many proteins that are incorrectly glycosylated fail to fold properly and/or fail to exit the ER, and are consequently degraded. On the other hand, there are many examples of proteins for which the prevention or alteration of glycosylation has little apparent consequence to their synthesis, folding, or delivery to a final location (see Tables I and II). Likewise, there are examples wherein removal of the oligosaccharides from a mature protein does not drastically alter sensitivity to proteolysis or immune recognition, nor their functions. These apparently contradictory observations exemplify a recurring theme: that while supporting evidence can be found for many

Table II. Effects of altered *O*-linked oligosaccharides on the biosynthesis, structure, transport and functions of glycoproteins

Protein	Effect of lack/alteration of oligosaccharides	Examples
GM-CSF[d]	Single *O*-linked chain protects against polymerization, denaturation, and loss of certain activities	(357)
Tracheal mucin glycoproteins[a]	Removal of sugar chains causes loss of water solubility; requires chaotropic agents or detergents for effective solubilization	(358)
Submaxillary gland mucin (molecular modelling studies)	Native and asialo-mucin are found to be highly extended random coils. Removal of the carbohydrate side chains causes collapse to chain with dimensions typical of denatured globular proteins	(359)
Intestinal brush border lactase-phlorizin hydrolase (LPH)[d]	Natural variant glycoform without *O*-glycosylation has identical K_m value but a 4-fold higher V_{max}	(360)
Arctic fish antifreeze glycoprotein[a]	*O*-Linked oligosaccharides required for freezing-point depression	(361)
Aspergillus niger glucoamylase[a]	Partial deglycosylation decreases thermal stability	(362)
Erythropoietin[c]	No effect of elimination on biosynthesis or biological activity. Small effect on secretion rate (?)	(199, 205)
Glycophorin A[a,d]	Polymorphic changes in amino acids surrounding three *O*-linked sites give rise to the MN blood group antigens. The intact, unmodified oligosaccharides are required for full antigenicity	(363, 364)
CD13 (aminopeptidase N)[c]	Natural variation in the extent of *O*-glycosylation. Anti CD-13 antibodies do not recognize all the forms	(365)
LDL receptor[c]	Multiple *O*-linked oligosaccharides: some are required for stable expression on the cell surface, but not required for LDL binding	(366–369)
ApoCII[c]	No effect on biosynthesis, secretion or lipoprotein particle formation	(370)
β-HCG[c]	No change in assembly or secretion, hormonal activity or immunoreactivity	(371, 372)

Note: unless otherwise stated, the proteins are of mammalian origin.
[a]Enzymatic or chemical removal of *O*-linked oligosaccharides.
[b]Prevention of *O*-linked glycosylation by competitive inhibitors (can have pleiotropic effects on other proteins in the same cell).
[c]Genetically engineered change in *O*-glycosylation.
[d]Natural genetic variant or defect.

Table III. Cell surface and matrix structure: examples of the 'structural', 'organizational' and 'barrier' functions

Oligosaccharide sequences	Interaction with	Examples of biological effects	Examples
Heparan sulphate chains of proteoglycans	Fibronectin, laminin, collagen, etc.	Organization of basement membrane and extracellular matrix. Filtering function of renal glomerulus. Cell adhesion to matrix	(53, 54, 58, 61, 66, 69, 373–377)
Chondroitin/dermatan sulphate chains of proteoglycans	Extracellular fibronectin	Deposition of fibronectin in the matrix: ?contact inhibition of cell growth	(57, 378–381)
Chondroitin sulphate and keratan sulphate chains	Multiple components of cartilage	Organization and tensile strength of cartilage	(53, 61, 70)
Dermatan sulphate chain of human blood protein pre-alpha inhibitor	Covalent cross-linking to heavy chain via esterification	A novel mechanism for cross-linking of two peptide subunits of a protein	(382)
Sialic acid and sulphate esters on glycoproteins	Other negatively charged residues	Determinant of net negative charge of cell surfaces and proteins: modulates cell–cell interactions and viscosity of secretions	(7, 40, 383, 384)
Glycolipids on epithelial cells	Other components of apical membranes, e.g. GPI anchored proteins	High local concentration on outer leaflet facing the lumen of organs: protective or barrier function?	(48, 79, 385–388)
Polylactosamine chains and/or β-Gal residues of laminin oligosaccharides	Bound by β-galactoside-specific 14 or 35 kDa lectins	Organization of matrix assembly? e.g. 14 kDa lectin induces loss of cell-substratum adhesion in developing myoblasts during differentiation and fusion into myofibres	(94, 96, 98, 105, 106, 389–392)
Polylactosamine chains of laminin oligosaccharides	Bound by 65 kDa elastin receptor in a β-galactoside-specific manner?	Organization of matrix elastin deposition?	(393, 394)
Glycophospholipid anchors of some membrane proteins. *N*-linked oligosaccharides of MHC class I proteins	Other membrane proteins?	Translational diffusion rates of proteins in the membrane altered markedly	(329, 395)
Gastric mucus (major component is gastric mucin, a glycoprotein with many *O*-linked sialylated and sulphated chains)	Water, ions and ?self-association	HCl, secreted by gastric glands, traverses the mucus layer without acidifying it because of 'viscous fingering'. HCl in the lumen (pH 2) cannot diffuse back to the epithelium because of the high viscosity of gastric mucus gel. Prevents the stomach from digesting itself	(396)

theories regarding oligosaccharide function, exceptions to each can equally well be observed.

In general, the development of these 'structural', 'protective' and 'stabilizing' functions during evolution should not have required the enormous complexities of structure that are found in naturally occurring oligosaccharide units. In keeping with this, inhibitors that only affect the later processing steps of oligosaccharide biosynthesis generally do not interfere with these types of functions. In these situations then, the oligosaccharides are analogous to the 'axle grease' of an automobile. While its absence would markedly affect the ability of the entire vehicle to function, the fine details of the composition of the grease should not be critical to the turning of the axle. Thus, while these roles of oligosaccharides are vital to the basic structure and function of the organism, they cannot explain the extensive structural diversity seen in nature.

The 'organizational' and 'barrier' functions

The extracellular matrix consists of a variety of glycoconjugates, each of which have been shown to have binding sites for various types of sugar chains, e.g. the heparin-binding domains of fibronectin and collagen. Recently, the role of such oligosaccharide-binding domains in the organization of the matrix has been clearly demonstrated *in vitro* (see Table III). Thus, for example, the chondroitin sulphate chain of the proteoglycan decorin is required for the organization of fibronectin in the extracellular matrix of Chinese hamster ovary (CHO) cells, which in turn dictates the phenotype of the cells in culture. In another case, the β-galactoside-binding function of a soluble lectin appears to be involved in the organization of elastin in the extracellular matrix. Similar functions have been proposed for the interaction between the polylactosamine chains of laminin oligosaccharides and certain β-galactoside-binding lectins. As shown in the other examples in Table III, oligosaccharides may also serve to create charge effects and domains in membranes.

Oligosaccharides as specific receptors for noxious agents: the 'traitorous' functions

It is abundantly clear that certain oligosaccharides can act as highly specific receptors for a variety of viruses, bacteria and parasites (see Table IV). They are also receptors for many plant and bacterial toxins, and serve as antigens for autoimmune and alloimmune reactions. In most of these instances, there is exquisite specificity for the sequence of the oligosaccharide involved. Thus, for example, the influenza viral haemagglutinins specifically recognize the type of sialic acid, its modifications and its linkage to the underlying sugar chain, while cholera toxin binds with great specificity to G_{M1} ganglioside and not to related structures. Likewise, incompletely synthesized (or partially degraded) oligosaccharides such as the Tn antigen can behave as autoantigens in man. There is little doubt about the extreme specificity of this group of 'functions' of oligosaccharides (see Table IV). In fact, this specificity has been used to great advantage by scientists investigating the expression of these sugar chains. However, to the organism that synthesized such oligosaccharides, there is little value in providing such 'traitorous' signposts to aid the access of pathogenic microorganisms or to permit damaging autoimmune reactions.

Oligosaccharide sequences that protect from microorganisms and antibodies: the 'masking' and 'decoy' functions

Just as certain oligosaccharides act as 'traitorous' signposts for microbial and immune attack, others can serve to abrogate these detrimental reactions (see Table V). In these cases, the addition of specific monosaccharides or modifications masks the sequences recognized by microorganisms, toxins or autoimmune antibodies. Thus, for example, the addition of a single *O*-acetylester to the 9-position of terminal sialic acid residues abrogates binding of the highly pathogenic influenza A viruses, and the extension of the oligosaccharide chain of GM_1 would prevent binding of cholera toxin. Likewise, the addition of galactose and sialic acid to the Tn antigen would abolish its autoimmune reactivity.

Oligosaccharide sequences on soluble glycoconjugates such as the mucins can also act as 'decoys' for microorganisms and parasites. Thus, pathogenic organisms attempting to gain access to mucosal membranes might first encounter their cognate oligosaccharide ligands attached to soluble mucins. Upon binding to these sequences, they could then be swept away by ciliary action, leaving the mucosal cells untouched. In these cases, the host may successfully turn the specificity of the pathogen receptor to its own advantage.

Oligosaccharides as specific receptors for 'symbiotic' functions

The possible evolutionary interplay between the 'traitorous' and 'masking' functions of oligosaccharides is discussed below. In contrast to these functions of sugar chains, there are some cases in which symbiotic relationships of animals with microorganisms appear to be aided by interactions involving specific oligosaccharides. Thus, certain commensal gut bacteria in animals and some root nodule-forming bacteria in plants appear to mediate their binding to host cell surfaces via specific sugar sequences. In these cases, inter-species recognition via oligosaccharides serves a function useful to both organisms involved. It is possible that such interactions are much more common and that they have not been carefully sought after.

Effects of oligosaccharides on the biological functions of proteins: 'on–off' and 'tuning' functions

There are several examples in which glycosylation can substantially modulate the interaction of peptides with their cognate ligands or receptors (see Tables I and VI). Some cell surface receptors for growth factors appear to acquire their binding functions in a glycosylation-dependent manner. Thus, the acquisition of function of a newly synthesized receptor may be delayed until it is well on its way to the cell surface. This might limit unwanted early interactions with a growth factor synthesized in the same cell. Glycosylation of a ligand can also potentially mediate such an 'on–off' or 'switching' effect. When the hormone human β chorionic gonadotrophin (β-HCG) is deglycosylated, it still binds to its receptor with similar

Table IV. Oligosaccharides as specific receptors for noxious agents, antigens for autoimmune responses, or as facilitators of infectious and malignant disease: the 'traitorous' functions

Oligosaccharide sequences	Recognition by	Biological effects	Examples
Terminal sialic acids	Receptors for a variety of virus haemagglutinins. Recognition is affected by linkage and/or substitutions of the sialic acids	First step in infectious process of viruses. Consequences range from lethal disease to mild self-limited infection	(73, 76, 397–422)
Terminal sialic acids	*Trypanosoma cruzi* trans-sialidase (has both neuraminidase and sialyltransferase activity)	Parasite utilizes host sialic acids and transfers them to its own surface, blocking antigenicity and complement activation	(423–430)
Specific gangliosides on cell surfaces	Receptors for several bacterial toxins e.g. *Vibrio cholerae* B subunits binds G_{M1} ganglioside	Cell binding and delivery of toxic subunits (e.g. A-subunit of *Vibrio cholerae*)	(95, 140, 141, 431–442)
Specific oligosaccharide sequences of glycolipids and glycoproteins on mucosal surfaces	Fimbrial proteins of pathogenic or commensal bacteria; binding receptors of certain mycoplasma, chlamydiae, protozoa and fungi	First step in infectious process of pathogenic organisms. Also helps to maintain localization of normal 'commensal' organisms?	(95, 140–144, 443–472)
Cell surface heparan sulphate chains	Receptor for herpes simplex virus	Initiates infection	(71, 473)
Traces of CMP-sialic acid ('serum resistance factor') found in blood	?Surface transferase on pathogenic *Neisseria gonorrhoeae*	Sialic acid is transferred to bacterial surface, blocking antigenicity and complement activation	(474–477)
N-Linked oligosaccharides on gastric parietal cell proteins	Required for reactivity of some autoantibodies in autoimmune gastritis and pernicious anaemia	Antibodies associated closely with mucosal atrophy, parietal cell loss—likely to be involved in pathogenesis	(478)
Erythrocyte and platelet glycoconjugates, e.g. polylactosamine chains on red blood cells ('i' antigen)	Antigens for spontaneously appearing 'cold agglutinins' and other autoimmune antibodies	Autoimmune destruction of cells, e.g. autoimmune haemolytic anaemia	(123, 479–485)
Incomplete oligosaccharide structures resulting from infectious agents or malignant transformation	Natural or induced antibodies against the incomplete structures, e.g. Tn antigen	?Autoimmune damage to cells and organs. Also beneficial because of anti-tumour effects?	(486–490)
Sialylated, fucosylated lactosaminoglycans on leukocytes	Ligands for selectin molecules on endothelial cells. System can work 'too well' under certains conditions of post-ischaemic reperfusion or inflammation	Toxic or inflammatory injury to tissues mediated by leukocytes exiting the bloodstream in excess	(83, 84, 86–93, 491–495)
Highly branched and sialylated *N*-linked oligosaccharides	Expressed in increased amounts on transformed cells	Enhances tumorigenicity and metastatic capability of tumour cells?	(121, 496–502)
Sialylated, fucosylated lactosaminoglycans on tumour cells	Ligands for selectin molecules on endothelial cells	Enhances metastatic capability of tumour cells via selectin-mediated binding?	(503–505)
Sialic acids and sialyloligosaccharides on many microbial surfaces	Blocks generation and reactivity of many antimicrobial antibodies, and facilitates binding of complement regulatory protein H	Protects microorganism from host antibodies and alternate pathway of complement	(506–511)
Neural glycosphingolipids	Naturally occurring monoclonal or polyclonal antibodies	Peripheral neuropathy (in some cases, it is not clear if the antibody is the cause or consequence of the disease)	(512–521)

affinity, but fails to transmit a signal via stimulation of adenylate cyclase. Thus, an agonist is converted into an antagonist; the precise mechanism of this effect remains unknown.

In most cases, such effects of glycosylation are not all or none, but are partial, or relative. In these 'tuning' functions, the biological activity of many glycosylated growth factors or hormones appears to be modulated over a significant range by the presence and extent of glycosylation. For example, the cytokine granulocyte/macrophage colony-stimulating factor (GM-CSF) is known to be most active in the unnatural non-glycosylated form derived from recombinant technology. However, naturally occurring preparations of GM-CSF contain a range of 'glycoforms', each of which shows substantial differences in binding affinity and signal transduction (see Tables I and VI). Another excellent example of this 'tuning' function is seen in the addition of polysialic acid to the neural cell adhesion molecule (N-CAM), which normally mediates homophilic binding with identical molecules on other cells (see Table XI). In the embryonic form, the oligosaccharides of this protein carry extended highly anionic chains of sialic acids that markedly reduce its capacity for homophilic binding. During development, the length of these polysialic acid molecules is altered, such that in the adult state they are much shorter. Thus, the adult N-CAM is capable of more effective homophilic binding, presumably because there is no longer a need for as much plasticity in the nervous system.

In other cases, the function of proteins can be 'tuned' not by oligosaccharides on the receptors or ligands themselves, but by

Table V. Oligosaccharide sequences that protect from microorganisms and immune reactions: the 'masking' functions

Oligosaccharide sequences	*Masks recognition of*	*Masks recognition by*	*Examples*
9-O-Acetylation	Terminal sialic acids	Influenza A and B viruses (generates recognition by other viruses)	(73, 74, 76, 403, 404)
9-O-Acetylation 4-O-Acetylation	Terminal sialic acids	Bacterial and viral sialidases	(73, 74, 76, 77, 522–528)
Terminal sialic acids on glycoproteins and cell surfaces	β-Gal and β-GalNAc residues	Asialoglycoprotein receptor Macrophage Gal/GalNAc lectin	(116, 120, 529)
Terminal sialic acids on *O*-linked oligosaccharides	Core *O*-linked oligosaccharides (T and Tn antigens)	Natural antibodies to T and Tn antigens	(486–490)
β-Gal residues	β-GlcNAc residues	Chicken hepatic lectin	(116, 530)
Cell surface heparan sulphate	Underlying 'activators'?	Alternate pathway of complement activation	(531–535)
Schistosoma mansoni miracida oligosaccharide	Underlying antigenic structures of the *Schistosoma*	The parasite, by the phagocytic cells of the invertebrate (snail) host	(536)
Heterogeneous oligosaccharides found on secreted mucins and in milk	Gut epithelial surface membrane oligosaccharides	By various microbial pathogens. Soluble molecules act as inhibitors or 'decoys'	(41, 537)

those on other neighbouring structures. An excellent example of this is seen in the modulation of growth factor receptors by gangliosides (see Table VI). The gangliosides are discrete and separate entities from the receptor proteins. However, it has been well demonstrated that the precise type of ganglioside that is present in a membrane can have a substantial effect on the tyrosine phosphorylation activity of the epidermal growth factor (EGF) receptor and the insulin receptor. While the precise mechanism of these effects is uncertain and some conflicting data have been published, it is clear that the specific oligosaccharide sequence of the ganglioside is required, rather than simply its net charge or size. Likewise, the polysialic acids of embryonic N-CAM have been shown to substantially blunt the binding of apposing cells via other unrelated receptor–ligand pairs, simply by physically expanding the space between cells. An extreme example of a 'tuning' effect of an oligosaccharide on a separate protein is that in which the heparin molecule modulates the action of the natural anticoagulant antithrombin III (see Table XI). In this case, the binding of highly specific heparin sequence to antithrombin III converts a very weak antithrombin into a potent anticoagulant. Such heparin sequences are presumed to have a significant anti-thrombogenic role on the surface of endothelial cells that are in contact with the blood stream.

Since these 'tuning' effects of oligosaccharides are usually partial and are rarely absolute, a sceptic might raise questions about their importance. However, when taken together, such partial effects could have a dramatic effect on the final biological outcome. Consider two different cell types that have the same number and types of growth factor receptors, and that are presented with the identical concentrations of the same growth factors. If the signal delivered to a cell was based only on the primary receptor–ligand interactions, there should be no difference in response between these two cells. However, if differences existed in the glycosylation state of the ligands, receptors or membrane gangliosides, each could have a significant positive or negative quantitative effect on the final signals delivered to the cell. Furthermore, glycosaminoglycan chains on the surface and in the matrix surrounding the cells could also modulate the action of each growth factor differently. Taken together, the combined effects on the different receptor–ligand-generated signals would be quite different for the two different cells. These differences would be further amplified by the fact that the intracellular signalling mechanisms of many receptors show significant overlap and cross-talk. Thus, the final effects of the same ligands at the same concentrations on the two different cells in question could be dramatically different. Thus, glycosylation can be a general mechanism for generating important functional diversity, while utilizing a limited set of receptor–ligand interactions.

As with most other functions of the oligosaccharides discussed so far, clear exceptions can be encountered. There are receptors whose ligand binding is not acquired in a glycosylation-dependent manner, and there are ligands whose binding and action is affected very little by the precise type of glycosylation found on itself or on its cognate receptor (see Table I). Once again, it is not possible to make a generalized theory based on the specific instances studied.

The 'sink' or 'depot' function of oligosaccharides

Another recently appreciated function of oligosaccharides appears to be that of acting as a protective storage depot for certain biologically important molecules (see Table VII). It has long been known that a variety of growth factors could be purified by affinity chromatography on immobilized glycosaminoglycan chains such as heparin. It now appears that the specific growth factors may bind tightly and specifically to certain glycosaminoglycan chains *in vivo*. This serves to localize the growth factors in question to the extracellular matrix surrounding the cells that need to be stimulated, and prevents diffusion of the factors to distal sites. There is also evidence that such a 'sink' can protect the growth factors from non-specific proteolysis, thus prolonging their active lives. A similar role may be played by the glycosaminoglycan chains found in secretory granules that appear to bind and protect protein contents after secretion, and to modulate their subsequent functions. As indicated in Table VII, there are other classic examples where oligosaccharides may act as 'sinks' or 'depots' for a variety of biological important molecules, ranging from water to complement regulatory proteins.

Table VI. Effects of oligosaccharides on the biological functions of proteins: 'on–off' and 'tuning' functions

Peptide(s)	Type of oligosaccharides	Biological effect(s)	Examples
Glycoprotein hormones, e.g. β-HCG	*N*-Linked oligosaccharides on the hormones	Required for signal transduction: removal results in conversion to an antagonist. Role in normal biology not fully defined	(126, 127, 170–174, 176, 178, 538)
Haematopoietic growth factors (e.g. GM-CSF and erythropoietin)	*N*-Linked oligosaccharides on the factors	Binding affinities and biological activities change substantially with differing degrees of glycosylation	(129, 195–197, 199–205, 208, 538)
Interleukin-1 and interleukin-2	Binding to high-mannose-type oligosaccharides on other molecules	Generates a surface membrane-bound form, of uncertain function. The cognate oligosaccharides show immunosuppressive actions *in vitro*	(539–543)
Various growth factors and cytokines, e.g. FGFs, GM-CSF, IL-3, Pleiotrophin, IL-7 and thymic stroma-derived T-cell growth factor	Binding to heparan sulphate chains (either free, or in the proteoglycan form)	Controlled release from matrix. Negative and positive regulation of growth-promoting effects? In some cases, heparan sulphate chains are required for high-affinity binding of factors by their receptors	(57, 60, 62–64, 72, 544–565)
Several proteases, protease activators and protease inhibitors (other than antithrombin III and heparin co-factor II, see Table XII)	Interaction with heparin/heparan sulphate chains	Varying degrees of positive or negative modulation of activities	(69, 566–573)
Jack bean concanavalin A (Con A)	*N*-Linked high-mannose-type oligosaccharide on the newly synthesized lectin	Keeps the precursor form inactive, until it is deglycosylated during later processing	(342, 343)
Some growth factor receptors[b,c,d]	*N*-Linked glycosylation-dependant activation: completion of disulphide bonds and native conformation requires partial processing of oligosaccharide (?)	Prevents premature association of growth factor made in the same cell with its cognate receptor?	(115, 294–298)
Some growth factor receptors (EGF receptor, insulin receptor)	Up- or down-regulation of tyrosine phosphorylation by specific gangliosides present in the same plasma membrane. Effects on growth control?	Permits modulation of the function of receptors without altering their number or affinity for the ligand. Role in normal biology not yet well defined	(47, 49, 574–582)
Certain intracellular protein kinases and phosphodiesterases	Modulation of phosphorylation by specific gangliosides. In some cases, specific phenotypic responses are seen in target cells	Modulation of signal transduction. Role in normal biology not yet well defined. Topological incongruity unresolved	(46, 583–597)
Cell surface integrins	G_{D3} and G_{D2} gangliosides	Calcium-dependent association appears to modulate adhesive function. Role in normal biology not well defined	(598–603)
Unknown	Specific types of gangliosides, particularly those with more sialic acids	Suppressive effects on cell proliferation in the immune response. May be important in the immunosuppressive effects of cancers. Role in normal biology not well defined	(51, 604–617)
Unknown	Neolacto- and G_{M3} gangliosides. Granulocytic or monocytic differentiation of myeloid precursors correlates with their expression	Exogenous addition of these gangliosides triggers the appropriate differentiation response. Role in normal biology not well defined	(52, 618–620)
Unknown	Different gangliosides added exogenously to neural cells in culture or administered to whole animals	Neurotrophic effects, promoting differentiation, potentiating healing, protecting from neurotoxic agents and promoting calcium fluxes. Role in normal biology not well defined	(45, 50, 621–647)
Transcription factors, cytosolic proteins and RNA polymerase	*O*-Linked GlcNAc residues at multiple sites	Indirect evidence suggests that expression may be rapidly regulated inversely with phosphorylation at the same sites—a mechanism for modulation of activities?	(145, 648, 649)
Glycophospholipid anchors of membrane proteins	Other membrane proteins? Signalling systems?	T-cell activation via different surface proteins requires GPI-anchors	(650–652)

Table VII. Maintaining local concentrations of specific molecules: examples of the 'sink' or 'depot' functions

Oligosaccharide sequences	Molecules bound and locally concentrated	Proposed biological effects	Examples
Matrix and/or basement membrane heparan sulphate chains	FGFs, GM-CSF and other cytokines in cell basement membranes or intercellular matrix	Maintains local concentration and availability of growth factor to the relevant cells. Protection of factors from proteolysis. Release upon injury to endothelium stimulates angiogenesis?	(57, 60, 64, 72, 544–560, 565, 653–655)
Cell surface and matrix heparan sulphate chains	Superoxide dismutase	Maintenance of local concentration of the enzyme in tissues?	(656)
Secretory granule proteoglycans	Binding to other components of the granule, e.g. enzymes	Permits packaging of materials into storage granules? Protects, localizes and modifies activity of bound molecules after secretion?	(657–661)
Chondroitin sulphate chain of macrophage colony stimulating factor (M-CSF)	Specific and selective binding of oligosaccharide to matrix Type V collagen	Maintains high local concentration of this form of M-CSF in bone marrow matrix and other sites of action?	(662)
Plasma membrane gangliosides	Calcium	Local increases in Ca^{2+} concentration, affecting receptor recognition processes?	(663)
Cell surface sialic acids	Facilitates high local binding and retention of complement regulatory protein H on cell surfaces	Prevents activation of the alternate pathway of complement on homologous surfaces (requires unmodified sialic acid side chain)	(510, 523, 532, 664–674)
Sialylated *N*-linked oligosaccharides in sea urchin	Calcium	Facilitates Ca^{2+} sequestration for deposition into the $CaCO_3$ skeleton	(675)
Sialic acid residues of fibrinogen	Calcium ('low-affinity' binding site)	At physiological Ca^{2+} concentrations, facilitates proper fibrin polymerization	(277)
Cell surface sialic acids on cardiac cells	Calcium	Removal of sialic acid markedly alters calcium currents into the cardiac cells	(676–678)
Surface sialic acids on synaptosomes	Sodium?	Removal of sialic acid markedly changes kinetics of Na^+-dependent uptake of the gamma-aminobutyric acid and D-aspartate	(679)
Sialic acids, uronic acids and sulphate esters on many glycoproteins and proteoglycans	Water	Help to create gel states of mucins and extracellular matrix	(1–3, 41, 54, 61, 65, 396)
Pig gastric mucus (major component is gastric mucin, a glycoprotein with many *O*-linked sialylated and sulphated chains)	Water and bicarbonate ions	Bicarbonate ions secreted by the gastric epithelium are trapped in the mucus gel, establishing a gradient from pH 1–2 at the lumen to pH 6–7 at the cell surface	(396)

'Intracellular trafficking' functions of oligosaccharides

The best understood example of such functions is the role of mannose-6-phosphate residues in targeting newly synthesized lysosomal enzymes to their final destination in the lysosomes (see Table VIII). In this case, the human disease states in which phosphorylation is deficient (I-cell disease and pseudo-Hurler polydystrophy) are characterized by a failure of lysosomal enzyme targeting in several cell types. This provides conclusive evidence for the importance of the oligosaccharide modification in mediating this important pathway. However, it is notable that even this elegantly precise function of oligosaccharides appears to have its exceptions: mannose phosphate is not absolutely required for the trafficking of lysosomal enzymes in some lower eukaryotes, nor is it essential in certain cell types in mammals. As indicated in Table VIII, many other endocytic receptors that recognize specific carbohydrate sequences have been described. However their role, if any, in intracellular trafficking (i.e. during the biosynthesis of glycoconjugates) has yet to be defined.

The role of oligosaccharides in regulating the 'clearance' or 'turnover' of proteins and whole cells: 'intercellular trafficking'

The effects of glycosylation on the stability of proteins to proteolysis has already been mentioned, and can presumably affect their turnover and half-life in the single cell. In the intact animal, recognition of oligosaccharide sequences by certain receptors can result in removal of the glycoconjugate or even the whole cell from the circulation. There have been several well-documented examples of the action of such 'intercellular trafficking' receptors (see Table VIII). Many of these interactions are highly specific for the oligosaccharide sequences recognized by the receptors, suggesting that their biological roles are equally specific. In several cases, rational theories have been put forward to explain the functions of these clearance pathways (see Table VIII). However, to date there have been very few naturally occurring mutants in these receptors described in an intact animal. This makes it difficult to obtain definitive proof of such functions.

Table VIII. Intra- and inter-cellular trafficking of proteins: 'targeting' and 'clearance' functions

Oligosaccharide sequences recognized	Lectin	Proposed role in protein trafficking	Examples
Phosphorylated high-mannose-type oligosaccharides on lysosomal enzymes and other proteins	Cation-independent M6P receptor Cation-dependent M6P receptor	Trafficking of newly synthesized lysosomal enzymes to lysosomes. Salvage of secreted phosphorylated enzymes?	(107–113, 680–696)
Exposed terminal β-Gal residues on mammalian plasma proteins	Asialoglycoprotein receptor	Clearance from circulation: determinant of half-life? Abnormalities in liver diseases, but significance unproven in normal	(116, 117, 120, 529, 697)
Exposed terminal β-GlcNAc residues on avian plasma proteins	Chicken hepatic lectin	Clearance from circulation: determinant of half-life?	(116, 530, 698)
Terminal 4-*O*-sulphated β-GalNAc residues on glycoprotein hormones	Specific receptor in the non-parenchymal liver cells	Rapid clearance from circulation: determinant of short half-life?	(118, 699, 700)
Mannose-rich oligosaccharides of endogenous and exogenous origin	Macrophage Man/Fuc receptor	Clearance of proteins from circulation? 'lectinophagocytosis' of pathogens?	(95, 97, 119, 701–708)
Gal/GalNAc-terminated oligosaccharides of endogenous and exogenous origin	Macrophage Gal/GalNAc receptor	Clearance of proteins from circulation? 'lectinophagocytosis' of pathogens?	(709–711)
N-Linked high-mannose-type oligosaccharides of endogenous and exogenous origin	Circulating 'core-specific' lectin	Opsoninization of pathogens, allowing complement activation and phagocytosis. Clearance of proteins from circulation?	(97, 119, 712–714)

'Hormonal' actions of oligosaccharides

It is now recognized that free oligosaccharides can themselves have biological effects in various systems, thus acting like hormones (see Table IX). The best documented examples are the 'oligosaccharins' of plants, which induce specific responses in a manner highly dependent on the structure of the sugar chain. Likewise, free high-mannose chains can have strong immunosuppressive effects in *in vitro* mammalian systems in a manner dependent upon the specific structure of the sugar chain. It is also likely that free heparin fragments released by certain cell types have effects on other cell types, acting perhaps via binding and internalization. However, in most of these cases the putative receptors for these molecules have not been identified, and the mechanisms by which they work remain uncertain. Many other less well defined oligosaccharides or glycopeptides with proposed biological effects are known, and are listed in Table IX.

Role of oligosaccharides in 'cell–cell and cell:matrix recognition'

Since all cells are covered with a dense coating of sugars, it has long been predicted that oligosaccharides must be critical determinants of 'cell–cell interactions'. In actual fact, there are relatively few examples in which such functions have been clearly defined (see Table X). Perhaps the best-documented example is that of the selectin family of receptor proteins that mediate the adhesion of leukocytes to endothelial cells (L-selectin), the recognition of leukocytes by stimulated or wounded endothelium (E-selectin), and the interactions of activated platelets or endothelium with leukocytes (P-selectin). In each case, the minimal carbohydrate ligands involved in recognition appear to be sialylated fucosylated sugar chains, such as sialyl Lewis^x and sialyl Lewis^a. However, biologically relevant recognition may require specific glycoconjugates that 'present' multiple copies of such oligosaccharides in a specialized fashion, i.e. in a proper spacing on the linear polypeptide chain, or in the proper three-dimensional context. In this regard, we have recently suggested that oligosaccharides that are very closely spaced together on the polypeptide might be packed tightly together, generating a 'clustered saccharide patch' for specific recognition. This would allow the generation of uncommon recognition markers utilizing common oligosaccharides. Alternatively, specific modifications of the oligosaccharides (e.g. sulphation) might be creating unique binding sites. There is also now substantial evidence that the binding of sperm to eggs involves the *O*-linked oligosaccharides on the zona pellucida glycoprotein ZP3, possibly by interacting with a surface β-galactosyltransferase. Other clear examples of cell–cell binding involving specific carbohydrates include CDw44, macrophage sialoadhesin and the B-cell lectin CD22β (see Table X). In many of these cases, rational theories can be constructed to explain the role of these cell–cell interactions. However, with the exception of the selectins, the specific biological significance of these recognition events has not been conclusively demonstrated in the intact animal.

A variation on this theme has been the proposal that carbohydrate–carbohydrate interactions may play a specific role in cell–cell interactions and adhesion. Several examples of such interactions have been presented and appear to show specificity for the structural details of oligosaccharides involved (see Table X). For example, there is provocative evidence that during murine embryogenesis, the stage-specific embryonic antigen (SSEA) which appears at the 16-cell stage is important in the compaction of the embryo, due to an Le^x–Le^x interaction. The affinities of such interactions can be measured with some difficulty and do not appear to be very strong. However, if the molecules in question are present in high copy number on the cell surface (e.g. glycolipids), the summing of a large number of relatively low-affinity interactions could result in a substantially higher avidity, sufficient for biological relevance. Such a 'velcro' effect may well be sufficient to mediate biologically relevant recognition.

In many of these cell–cell interactions, protein–protein binding phenomena clearly also play critical roles, e.g. the LFA-I/

Table IX. Biologically active oligosaccharides and glycopeptides: 'hormonal' actions

Oligosaccharide sequences recognized	Target tissues or cells/cognate receptor	Reported biological effects	Examples
Specific β-glucan oligosaccharides of *Phytophthora* fungal cell walls	Various plants Unknown receptor	Elicitor of production of phytoalexins (plant antibiotics against fungi)	(136, 137, 715–717)
Polygalacturonic oligosaccharides of plant cell walls	Tomato and potato Unknown receptor	Elicitor of production of phytoalexins. Induces phosphorylation of specific membrane proteins and morphological changes in cultured tissues	(137, 718)
Exopolysaccharide of *Rhizobium* species. Specific sulphated, acylated or fucosylated sequences	Alfalfa or soybean root cells Unknown receptor	Elicits root nodulation in host: determinant of symbiotic relationship between *Rhizobium* and plants	(138, 139, 719–724)
Oligosaccharides derived from sycamore cells	Tissue culture 'callus' of tobacco cells or duckweed cells. Unknown receptor	Selective induction of vegetative budding or floral growth: hypothesized to modulate organ development in the intact plant	(725)
Free heparin/heparan chains from adjacent cells, e.g. smooth muscle cells and endothelial cells	Unknown receptor in nucleus? Eventually works via c-*fos* and c-*myc* in endothelial cells	Inhibition of cell growth	(60, 726–736)
Glucosamine-containing oligosaccharide(s)—derived from glycosylphosphatidyl inositol?	Various mammalian cell types Unknown receptor(s)	Proposed second messengers for some Interleukin-2, NGF, and insulin-mediated signal transduction events	(80, 737–749)
Sialylated fucosylated glycopeptide from brain cells	Various animal cell types Receptor of 150 kDa?	Growth inhibition of a variety of cell types	(750–752)
A glycopeptide from malignant tumour effusions. An acceptor for galactosyltransferase	Various tumour cell types Oligosaccharide required for binding: receptor unknown	Growth inhibition, antitumour effects	(753, 754)
A sialoglycopeptide circulating in patients with sepsis or trauma	Unknown	Induces endogenous proteolysis in rat muscle, similar to that occurring in patients	(755) (756–759)
Free sialylated *N*-linked oligosaccharides released from trout egg glycoproteins during oogenesis	Unknown	Unknown. Large quantities suggest a specific function	

Table X. Lectin–carbohydrate and carbohydrate–carbohydrate interactions: examples of 'cell:cell and cell:matrix recognition'

Lectin	Oligosaccharide sequences recognized	Proposed biological functions	Examples
E-Selectin (ELAM-1)	Sialylated fucosylated polylactosaminoglycans on unknown leukocyte glycoconjugates	Primary adhesion of granulocytes, monocytes and certain lymphocytes to acutely or chronically inflamed endothelium	(760–771)
P-Selectin (GMP-140/PADGEM/CD62)	Sialylated fucosylated polylactosaminoglycans (on a specific myeloid glycoprotein?) (sulphated ligands as well?)	Primary adhesion of granulocytes, monocytes and certain lymphocytes to activated platelets or endothelium	(763, 766, 768, 770, 772–780)
L-Selectin (LAM-1, MEL-14 antigen, LHR)	Sialylated, fucosylated, sulphated oligosaccharides (on specific glycoproteins?) (other sulphated ligands as well?)	Adhesion of granulocytes to inflamed endothelium and of naive lymphocytes to endothelium of high-endothelial venules: a determinant of lymphocyte trafficking	(770, 771, 781–787)
CD44 (Hermes, Pgp-1)	Hyaluronic acid	Adhesion of many cell types to endothelial cells and matrix. Additional determinant of lymphocyte trafficking	(788–795)
CD22β lectin of B-lymphocytes	α2-6-linked sialic acids on lactosamine units of specific glycoproteins, e.g. CD45	Early step in interactions of B-cells with activated T-cells or activated B-cells. Cross-linking of CD45?	(796–800)
Macrophage Gal/GalNAc receptor	Terminal β-Gal or β-GalNAc residues on blood cells or pathogens	Clearance from circulation: determinant of half-life?? Phagocytosis of pathogens?	(709–711)
Macrophage sialic acid-specific receptor	Sialic acids on surface glycoconjugates, in the sequence Sia α 2-3Gal β 1-3GalNAc	Interaction of bone marrow macrophages with haematopoietic precursors and lymph node macrophages with lymphocytes?	(801–804)
Kupffer cell-specific Gal/Fuc receptor	?Specific oligosaccharide structures in liver matrix	??Mechanism of localization and retention of Kupffer cells in liver	(805–808)

Table X. *continued*

Lectin	Oligosaccharide sequences recognized	Proposed biological functions	Examples
Surface β1-4 galactosyltransferase	GlcNAc-terminating oligosaccharides on target cells? Transferase acts as a lectin?	Sperm–egg receptor function? Inducer of acrosome reaction? Role in cell migration during development and tissue organization? Role in neurite extension? Role in tumour metastasis?	(147, 809–821)
Unknown, on mammalian sperm	α-Linked Gal residues on *O*-linked oligosaccharides of egg protein ZP3	Sperm–egg recognition. Inducer of acrosome reaction? Competing theory with surface β-galactosyltransferase	(822–824)
Cell surface/soluble β-galactoside-binding lectins in a variety of cell types	β-Galactoside and/or polylactosamine residues on other cells or in the matrix	Implicated in cell–cell and cell–matrix interactions in development and tissue organization. Also may serve as receptors for certain immunoglobulins. Role in tumour metastasis?	(94, 96, 104–106, 390, 825–838)
Cerebellar soluble lectin	31 kDa endogenous glycoprotein ligand?	Mediates contact guidance of neuron migration by astrocytes?	(99, 100, 839–843)
Extracellular matrix proteins (e.g. laminin, fibronectin, thrombospondin)	Binding to heparan sulphate chains on cell surface proteoglycans	Role is mediating cell adhesion, differentiation, spreading or invasion	(376, 844–850)
Several extracellular matrix proteins (e.g. laminin, thrombospondin) membrane receptors (e.g. P-selectin) and soluble proteins	Binding to 3-*O*-sulphated galactosylceramide (sulphatide)	Role in mediating cell attachment and/or differentiation?	(774, 851–861)
Macrophage migration inhibitory factor	Specific cell surface ganglioside	Lymphocyte cytokine that modulates macrophage migration into tissues?	(862, 863)
Unknown	*N*-Linked glycans, in some cases carrying polylactosamines	Complex literature suggesting roles for oligosaccharides in interactions between lymphocytes, and between natural killer cells and their targets	(101, 864–868)
Unknown receptor in epithelium of sandfly midgut	Lipophosphoglycan of *Leishmania* only in non-infective stage promastigotes	Allow stage-specific adhesion of non-infective stage promastigotes and selective release of infective stage promastigotes	(869)
Gal-specific lectin of *Bradyrhizobium japonicum*	Unknown ligand on plant cells	Facilitates symbiotic interactions?	(870, 871)
Unknown receptor on *Capnocytophaga ochracea*	Specific hexasaccharide repeat from cell wall of *Streptococcus sanguis*	Co-aggregation of the two bacterial strains is implicated in formation of dental plaque	(872)
CARBOHYDRATE 1	CARBOHYDRATE 2		
Multimillion molecular weight aggregation factor (MAF)	MAF	Mediates cell–cell recognition in the sponge *Microciona prolifera*	(873, 874)
Xanthan gum polysaccharide	Carob gum polysaccharide	Intermolecular binding mediates gelation and ?binding of *Xanthomonas* bacteria	(875)
Hyaluronan	Chondroitin sulphate	Specific inter-molecular interaction–significant in matrix organization? Involvement of protein not ruled out	(876)
Bacteroides fragilis capsular polysaccharide A	*B.fragilis* capsular polysaccharide B	Strong ionic interactions create a complex, aggregated polymer—a virulence factor	(877)
Lewis^x structure	Lewis^x structure	?Mediates compaction of the morula-stage embryo	(878–880)
G_{M3} ganglioside	G_{g3} or Lac-Cer glycolipids (carbohydrate–carbohydrate interaction)	?Mediates interaction between different cell types	(881–883)

I-CAM interaction in leukocyte–endothelium binding (87). However, these interactions appear to require activation of the cells and do not seem to work well under the shear forces present in the flowing bloodstream. Several lines of evidence indicate that oligosaccharide–protein interactions provide the initial specificity for the interaction, and the strength and permanence of the association is then mediated by protein–protein interactions (reviewed in 87–93). This would allow the parsimonious use of a limited set of protein–protein interactions as a generic glue for a variety of cell–cell interactions, while

leaving the specificity to the diversity of oligosaccharide structures.

Such intercellular interactions should be most important during embryonic development. The number of genes (50 000–100 000) available in the genome of a mouse cannot possibly account for the numerous specific steps required for complete murine embryogenesis if a different gene was required for a each step. However, a set of glycosyltransferases expressed in various combinations could provide a wide variety of different potential ligands for cell–cell interactions. The frequent demonstration of regional, spatial and gradient expression of carbohydrate structures during embryonic development strengthens the notion that such specific interactions are indeed important at various steps in development. However, proof that such interactions are important requires the availability of mutants with genetic defects in glycosylation.

Do any general principles emerge?

The discussion so far makes it clear that the oligosaccharide units of glycoconjugates have many and varied functions. It also leads to the conclusion that while all of the theories about their functions appear to be correct, exceptions to each can also be found. A corollary of this conclusion is that it is difficult to predict *a priori* the functions of a given oligosaccharide on a given glycoconjugate. Fortunately, some other worthwhile principles do emerge from this analysis.

Temporal and spatial differences in the expression of oligosaccharides: the same structure can have multiple roles

The expression of specific types of glycosylation on different glyconjugates in different tissues at different times of development implies that these structures must have diverse and different roles in the same organism. For example, mannose-6-phosphate-containing oligosaccharides were first described on lysosomal enzymes and are clearly involved in targeting them to lysosomes. However, since that time, mannose-6-phosphate-containing oligosaccharides have been found on a variety of apparently unrelated proteins, including proliferin (1038), thyroglobulin (947, 948), the EGF receptor (1039) and the transforming growth factor β (TGF-β) precursor (895). While the significance of these observations is uncertain, they raise the possibility that mannose-6-phosphate-containing oligosaccharides have other biological roles. Likewise, the sialylated fucosylated lactosamines critical for recognition by the selectins are also found in variety of other tissues, where the selectins are unlikely to be functioning (16, 17). The polysialic acid chains that appear to play such an important role in embryonic N-CAM have also been found on proteins as diverse as an egg jelly coat protein and a sodium channel protein (18). Likewise, 9-*O*-acetylation of sialic acids is found on a variety of different glycoconjugates, in a variety of different tissues at different times in development (7, 74, 76).

Given that oligosaccharides are post-translational modifications, these observations should not be entirely surprising. Once it is expressed in an organism, the same oligosaccharide modification could have independently evolved several distinct usages in different tissues and at different times in development. If any one of these functions were vital to the survival of the organism, then the transferase mediating the expression of the oligosaccharide structure would be conserved in evolution, thus perpetuating the less important situations where it was expressed as well. It is even conceivable that expression of a particular structure on a particular glycoconjugate might be of no positive consequence whatsoever in that particular situation. However, the transferase responsible for this structure may have been selected because of its vital contribution to the function of an entirely different glycoconjugate. As long as there was no strongly negative consequence for the first glycoconjugate, its expression might persist in that situation and be considered 'revenue neutral' for the organism.

Can the interplay between 'traitorous' and 'masking' functions result in the formation of 'junk' oligosaccharides?

The 9-*O*-acetylester group that abrogates binding of the highly pathogenic influenza A viruses to sialic acids simultaneously generates a specific binding site for the less pathogenic influenza C virus and coronaviruses (see Tables IV and V). Such *O*-acetylated acids are frequently found on mucosal surfaces of mammals. Perhaps the mammalian organism first attempted to mask the sialic acid receptor for the highly pathogenic influenza A virus by adding an *O*-acetyl group to it. However, subsequent selection could have resulted in the appearance of microorganisms (influenza C and coronaviruses) capable of binding specifically to the 'masking' structure.

Since microorganisms and parasites evolved in parallel with their multicellular hosts, they may have had to constantly adapt themselves to bind to each new 'masking' structure evolved by the host. In response, the host organism may have found it most efficient to generate new masking structures, perhaps because the existing structure had already evolved a vital function elsewhere within the organism. Having committed itself to this course of action, the host would then be left with no choice but to keep the underlying 'scaffolding' upon which the latest 'mask' was placed. Thus, yet another layer of complexity would have been added to its oligosaccharides. Such cycles of interaction between microorganisms and hosts could explain in part some of the extremely complex and extended sugar chains found on mucosal surfaces and secreted mucins. It also leads to the possibility that 'junk' oligosaccharides do exist akin to 'junk' DNA. While serving a general (and important) function as a scaffolding, they may have no other specific definable role.

Inter-species variations in glycosylation

The existence of species-specific variations in glycoconjugate structure indicates that some oligosaccharides do not play fundamental and universal roles in all biological systems. For example, the glycolipids of red blood cells from various mammalian species show striking differences both in the primary sequence of the glyconjugate and in the type of sialic acid on the acidic glycolipids (see Table XII). Likewise, when the *N*-linked glycosylation on a conserved protein such as gamma glutamyl transpeptidase was examined from a variety of species, marked differences were seen in the sequence of the sugar chains (35). Such variations between species in the glycosylation of similar proteins or cells imply that these sugar chains cannot be crucial for the basic functions of these proteins or cells. On the other hand, such diversity in glycosylation could

Table XI. Unique or unusual types of glycosylation more frequently mediate specific biological roles

Molecule(s) modified	Unusual or unique type of glycosylation	Proposed biological role(s)	Reviews and examples
Lysosomal enzymes	Mannose 6-phosphate on high-mannose-type oligosaccharides	Intracellular trafficking of enzymes by binding to mannose 6-phosphate receptors	(107–112, 681, 683, 884–894)
TGF-β precursor	Mannose 6-phosphate ?in high-mannose-type oligosaccharides	Intercellular traffic of precursor to permit activation in acidic endosomes?	(895)
Neural cell adhesion molecule (N-CAM)	Polysialic acid	Inhibition of homotypic binding between N-CAM molecules and general inhibition of intercellular adhesion involving other binding systems. Positive effects also?	(18, 896–907)
Endothelial and mast-cell heparan sulphate proteoglycans	3-*O*-sulphation of selected GlcNAc residues in specific pentasaccharides	Antithrombin III binding and activation, resulting in anticoagulation	(58, 62, 908–913)
Extracellular matrix dermatan sulphate proteoglycans	4-*O*-S-GalNAc and 2-*O*-S-GlA residues in three sequential disaccharide repeats	Heparin co-factor II binding and activation, resulting in anticoagulation	(914, 915)
Cell surface and matrix heparan sulphate	2-*O*-S-IdoA residues within defined sequences	Required for high-affinity binding of bFGF to its cell surface receptor	(72, 558)
Pituitary glycoprotein hormones	GalNAc 4-SO_4 terminating antennae of *N*-linked oligosaccharides	Effects upon turnover, plasma half-life and bioactivity of the hormones	(118, 130, 699, 700)
Rhizobium polysaccharides	Sulphation and acylation of β1-4-linked glucosamine residues	Symbiotic host specificity: elicitation of root hair deformation and nodulation	(138, 139, 719–724)
Specific glycoproteins on myeloid and endothelial cells	Sialylated, fucosylated (and sulphated?) lactosaminoglycans	Primary recognition motifs for the selectin family of cell adhesion molecules	(83, 84, 86–93, 760–768, 768–771, 773, 777, 778, 780–785)
N-Cadherin	GalNAc-phosphodiesters on *O*-linked oligosaccharides	?Involved in modulating adhesive functions of the cadherin in neural development	(916–921)
Laminin	Polylactosaminoglycans on *N*-linked oligosaccharides	Binding to soluble β-galactoside-binding lectins (galaptins): matrix organization?	(390, 825, 834, 922–924)
Placental fibronectin	Polylactosaminoglycans on *N*-linked oligosaccharides	Decreased binding to gelatin. ?Altered binding functions in the placenta	(925)
Endothelial thrombomodulin	Chondroitin/dermatan sulphate chain attached to a fraction of the molecules	Negative regulation of all of the anticoagulant activities of thrombomodulin	(926–930)
Cytosolic parafuscin	Glc-P-Man on *O*-linked oligosaccharides	Very rapid changes in phosphorylation accompanying activation and exocytosis?	(931, 932)
Gangliosides of nervous system and neural crest cells	*O*-Acetylation of a terminal α2-8-linked sialic acid residue on polysialosyl units	Expression is temporally and spatially regulated. Abnormalities seen in transgenic mice with decreased *O*-acetylation in certain tissues	(933–940)
Several neural cell adhesion molecules	HNK-1 epitope/L1 epitope: sulphated glucuronic acid residues?	Some evidence for direct involvement in cell:cell adhesion	(941–946)
Thyroglobulin	βGal 3-SO_4 βGlcNAc 6-SO_4 Mannose 6-phosphate	?Role in uptake and/or processing of thyroglobulin into thyroid hormones	(947–952)

certainly be involved in generating the many obvious differences in morphology and function that are observed between species. Such differences could also reflect differing selection pressures resulting from different pathogens that infect the different species.

Intra-species variations in glycosylation

Genetic polymorphisms with no known biological consequence are quite common in proteins. For example, in Sweden alone, at least nine different albumin variants were found, with a combined prevalence of 1:1700 in the population (1046). The genetic polymorphisms in glycosylation that are recognized as 'blood-groups' (discovered because of the unnatural practice of blood transfusion) also have limited consequences for the normal biology of humans. Similar intra-species polymorphisms have been observed between the sialic acids on red blood cells or hepatocytes in different in-bred strains of mice and dogs (see Table XII). It is clear that substantial intra-species polymorphism in oligosaccharide structure can exist without obvious reason. However, these polymorphisms may be of far more importance in the wild state, where protection against certain microorganisms or other noxious agents could prove to be of survival value to a segment of the population expressing a specific oligosaccharide structure. In some cases, the pathogens that originally selected for such polymorphisms may have disappeared from the environment in the very recent evolutionary past, leaving behind the unexplained polymorphism.

Table XII. Genetic defects or polymorphisms in glycosylation are uncommon in higher animals, but have variable consequences

Genetic defect/variation	Basic defect in glycosylation	Biological consequence(s)	References
Partial or complete deficiency of lysosomal enzyme: UDP-GlcNAc GlcNAc-phosphotransferase	Partial or complete failure of phosphorylation of mannose residues on lysosomal enzymes	Partial or complete failure of lysosomal enzyme trafficking in I-cell disease (mucolipidosis II) and Pseudo-Hurler polydystrophy (MLIII)	(107–111, 953–959)
Partial deficiency of UDP-GlcNAc: α-mannoside GlcNAc transferase II or *processing α-mannosidase II*	Incomplete processing of *N*-linked oligosaccharides: decreased addition of *polylactosamine units*	Hereditary erythrocytic multinuclearity with positive acidified serum test (HEMPAS), *also known as congenital dyserythropoietic* anaemia type II	(131, 960–965)
Partial deficiency of xylosylprotein 4-β-galactosyltransferase	Decreased production of glycosaminoglycan chains with core Galβ1-4Xyl linkage	Progeroid syndrome with delayed mental development, and multiple connective tissue abnormalities	(966, 967)
?Decreased conversion of GDP-fucose to GDP-mannose (general fucose deficiency)	Low levels of GDF-fucose, low levels of fucose on all glycoconjugates	Leukocyte adhesion deficiency type II. Low fucose on many glycoconjugates results in lack of ligands for selectins, and poor leukocyte adhesion. Bombay Blood group type. Infections, short stature, mental abnormalities, skeletal defects	(968)
?Deficiency of PAPS: Lactosaminoglycan sulphotransferase(s)	Decreased sulphation of keratan sulphate in cornea (?) and other tissues	Macular corneal dystrophy type I: progressive clouding of the cornea resulting in blindness	(969, 970)
Defects at multiple steps in assembly of the glycophospholipid (GPI) anchor precursor (?acquired genetic defect in haematopoietic stem cell)	Lack of pre-formed donor for GPI-anchoring of proteins	Paroxysmal nocturnal haemoglobinuria (PNH): failure of GPI anchoring/secretion of several cell surface proteins on blood cells—haemolytic anaemia, increased infections, progression to malignancy	(132, 971–978)
Mosaic deficiency of UDP-galactose: GalNAc 3-β-galactosyltransferase affecting a *subset of cells (usually acquired)*	Decrease in Galβ1-3GalNAc of *O*-linked oligosaccharides. Increase in GalNAc-O-Ser (Tn antigen)	Polyagglutinability of red cells by all normal human sera: variable haemolytic anaemia. Can be seen as a precursor to leukaemias	(486, 979–982)
Galactose-1-phosphate uridyltransferase deficiency (galactosaemia)	Defect primarily affects low molecular weight pools of galactose-related molecules. However, some abnormal galactosylation of complex carbohydrates is also noted	May account for some of the abnormalities that persist when patients are treated with galactose-free diets	(983, 984)
Decreased synthesis of 3′-phosphoadenosine 5′-phosphosulphate (PAPS)	Decreased sulphation of glycosaminoglycans and abnormalities in proteoglycans	Brachymorphic mice with skeletal abnormalities (because of partial defect, tissues with the highest sulphate requirement, e.g. cartilage, are most affected)	(985–987)
Hereditary opsonic defect	Point mutation in serum mannose-binding protein	Heterozygous state causes low opsonization of pathogens. Increased infections in childhood	(988–990)

Terminal sequences, unusual structures and modifications of oligosaccharides are more likely to mediate specific biological roles

It is reasonably clear that the biological roles of oligosaccharides can range from those that are trivial to those that are critical for the development, growth, function or survival of an organism. The challenge then is to predict which sugar chains are likely to mediate the more specific or crucial biological roles. Review of the matter suggests that terminal sugar sequences, unusual structures or modifications of the oligosaccharides are more likely to be involved in such specific roles (see Table XI). For example, the high-mannose oligosaccharide structures of lysosomal enzymes are identical to those found on a wide variety of proteins, ranging from the immunoglobulin IgM in mammals to the lectin soybean agglutinin in plants. It is reasonable to suggest that such a widely expressed structure is less likely to be involved in mediating specific biological functions. On the other hand, the addition of phosphomonester residues to one or two of the mannose units results in the generation of the highly specific phosphomannosyl recognition marker that dictates trafficking of the enzyme to the lysosome. Likewise, segments of the common heparin/heparan disaccharide repeating unit are converted into specific ligands for antithrombin III or basic fibroblast growth factor (bFGF) by a highly ordered series of epimerization and sulphation reactions. Similar, although less conclusive arguments can be made for other modifications such as polysialic acids, *O*-acetylation of sialic acids, polylactosaminoglycan chain formation and outer chain fucosylation (see Table XI).

Table XII. *continued*

Genetic defect/variation	Basic defect in glycosylation	Biological consequence(s)	References
IgG cryoglobulin	*N*-Linked glycosylation in first heavy chain hypervariable region	Precipitation of immunoglobulin in the cold, leading to vascular problems	(991)
Type I procollagen in a case of osteogenesis imperfecta	?New *N*-linked glycosylation site in carboxy-terminal peptide	Cause of increased fragility of bones?	(992)
Saposin B in a case of congenital deficiency	Point mutation eliminates a new *N*-linked glycosylation site	Unmasking of proteolytic site causes rapid turnover, resulting in deficiency	(993)
Haemophilia A variant	Point mutation creates a new *N*-linked glycosylation site	Decreased function of Factor VIII, leading to bleeding disorder	(994)
C1 inhibitor Ta	Additional glycosylation site created by three-base deletion	Type II hereditary angioneurotic edema	(271)
Albumin Redhill	New glycosylation site and altered signal peptidase cleavage	No obvious phenotype(?)	(995)
Protein S (Heerlen polymorphism)	Loss of glycosylation site	No change in protein C binding. No phenotype	(290)
Deficiency of UDP-Gal: 3-α-galactosyltransferase (in humans, apes and Old World monkeys)	Marked decrease of Galα1-3Galβ1-4GlcNAc sequences terminating glycoprotein and glycolipid oligosaccharides	No obvious abnormality results. All humans have a natural antibody (up to 1% of circulating IgG) against Galα1-3-Galβ1-4GlcNAc sequences	(996–999)
Polymorphic expression of active or null alleles for UDP-Gal: *H-precursor* 3-α-galactosyltransferase (B-enzyme) and UDP-GalNAc: *H-precursor* 3-α-*N*-acetylgalactos-aminyltransferase (A enzyme)	Polymorphism expression of A and B and *O blood groups structures terminating* glycoprotein and glycolipid oligosaccharides	No obvious abnormality results. Humans *have natural antibodies against* the blood group sequences that they do not express	90, 123, 148, 1000–1003)
Polymorphic expression of Sd^a antigen in humans	Polymorphism in expression of GalNAcβ1-4[NeuAcα2-3]Galβ1-4GlcNAc	No obvious abnormality results	(1004, 1005)
Polymorphic expression of UDP-Gal: Galα1-4 galactosyltransferases (the P blood group system). Some individuals lack the enzyme(s) (blood group p)	Polymorphism in the expression of P, P1 and P^k blood group structures terminating glycoprotein and glycolipid oligosaccharides	No obvious abnormality results. Individuals with some P blood groups are at greater risk for urinary tract infections with *E.coli* carrying specific P-fimbriae, because they *express the cognate oligosaccharide ligand* on their urothelial surfaces	(140, 141, 444–446, 449, 450)
Primary enzymatic basis not fully defined	Polymorphic expression of *N*-acetyl and *N*-glycolyl-neuraminic acid on the erythrocyte gangliosides of dogs and cats	No grossly obvious consequences in dogs. Possibly related to the geographic co-migration of dogs with humans, and subsequent breeding patterns. In cats, this accounts for a major blood group system	(1006–1008)
Differing levels of expression of ganglioside biosynthetic enzymes *in* the livers of different inbred strains of mice	Differences in the overall pattern of *ganglioside expression in the liver and other* organs	No grossly obvious consequences	(1009–1012)

Note: unless otherwise stated, the defects reported in this table were found in humans.

Unusual oligosaccharides or modifications are also more likely to arise from interactions with microorganisms and other noxious agents

The constant balance between the 'traitorous' and 'masking' functions of oligosaccharides has been discussed above (see Tables IV and V). In most cases, it is the terminal or outer sugars and their modifications that are involved in these life-and-death interactions. Consequently, while such structures may be more involved in specific biological roles within the organism, they are also most likely to vary as a result of host–pathogen interactions. However, the two functions need not be mutually exclusive. For example, it is possible that while *O*-acetylation of sialic acids on mucosal surfaces may play a protective role in host–microbial interaction, the temporal and spatial gradients of expression of *O*-acetylation found in the developing nervous system may play important roles in the process of development in the brain. The challenge then is to predict and sort out which of these two completely distinct roles are to be assigned to a given oligosaccharide structure.

In some cases of sporadic autoimmune reactions to oligosaccharides, the antigenic structures are normally present in adult tissues (e.g. antibodies against peripheral nerve glycolipids seen in some individuals with multiple myeloma). However, there are examples of oligosaccharide structures which when expressed postnatally by the organism result universally in an immune response. The best examples in humans are the conversion of *N*-acetylneuraminic acid to *N*-glycolylneuraminic acid (1040, 1041) and the expression of Galα1-3 Gal sequences (see Table XII). In these cases, the structures are not expressed in normal adults, but can appear in

disease states such as cancer, resulting in immune reactions due to newly induced or pre-existing antibodies. In at least one case (*N*-glycolylneuraminic acid), it is clear that expression actually does occur in the normal fetus, but is then suppressed post-natally in the normal adult. The oligosaccharides in question evidently must have no normal functions in the adult. However, it is likely that their expression in the fetus is a required event and is a case of ontogeny recapitulating phylogeny.

Is there a common theme to the varied functions of oligosaccharides?

We have reviewed the evidence that all of the diverse theories regarding the functions of oligosaccharides are correct, but that exceptions to almost every theory can also be found. In the final analysis, the only common feature of all of these functions is that they either mediate 'specific recognition' events or that they provide 'modulation' of biological processes. In so doing, they help to generate the functional diversity that is required for the evolution and development of different types of cells, tissues, organs and species. There is a limited number of genes available in the genome for the generation of such diversity. Thus, it should not be surprising that an oligosaccharide structure resulting from the action of a single gene product could be utilized to generate a wide variety of functions in different tissues at different times in the life cycle of the organism. However, even complete knowledge about the structure, biosynthesis and expression of a particular type of structure does not necessarily give us clues to its specific functions. The challenge before us is to design experiments to differentiate between the trivial and crucial functions mediated by a given oligosaccharide.

Approaches to uncovering specific biological roles of oligosaccharides

Some functions of oligosaccharides are discovered serendipitously. In most cases, the investigator who has elucidated complete details of the structure and biosynthesis of a specific oligosaccharide is still left without knowing its functions. If it is possible to make educated guesses about the role of the oligosaccharide in question, this can sometimes lead to definitive experiments. However, conclusive proof of the biological roles of an oligosaccharide sequence often requires analysis of mutants that are defective in such a structure. It is therefore useful to consider the lessons that have been learned to date by studying such mutants.

Genetic or acquired defects in glycosylation are easily obtained in cultured cells, but have somewhat limited consequences

The essential pathways of biosynthesis of most of the major classes of oligosaccharides have now been worked out and involve a large number of gene products, including many families of glycosyltransferases. Tissue culture cell lines with mutations in a variety of specific steps in the biosynthesis of *N*-linked oligosaccarides, glycosaminoglycans, *O*-linked oligosaccharides and glycophospholipid anchors have been obtained, including some with defects in very early steps in the biosynthetic pathways (for examples, see 30,71,1043,1044). Mutants affecting the biosynthesis of dolichol sugars, sugar nucleotides or sugar nucleotide transport into the Golgi apparatus have also been obtained, and have pleiotropic effects on the biosynthesis of multiple types of glycoconjugates in the same cell. Likewise, cell lines can be grown in the presence of global inhibitors of the biosynthesis and processing of several types of oligosaccharides (for example, see 1042). In most of these situations, the abnormalities in glycosylation seem to have limited consequences to the growth and maintenance of these tissue culture cell lines. This suggests that many (though not all) aspects of glycosylation are of limited importance in the day-to-day housekeeping functions of the single cell, when it is in a protected environment, under optimal conditions of growth. Of note, however, some of these mutants do show alterations in density-dependent growth inhibition and others demonstrate changes in tumorigenicity or metastatic behaviour when injected into athymic mice (1045). This suggests that many of the more specific biological roles of oligosaccharides need to be uncovered by studying mutations in the intact multicellular organism.

Genetic defects in glycosylation are rare in intact organisms, but have highly variable consequences

In contrast to the situation *in vitro*, genetic defects in glycosylation are surprisingly rare in intact organisms. There are few other biochemical pathways in which naturally occurring mutants in mouse and man are so uncommon. In the few instances in which glycosylation mutants have been observed in intact complex multicellular organisms, the consequences have been highly variable (see Table XII). In humans, the effects of genetically altered glycosylation range from severe lethal diseases such as I-cell disease to apparently unremarkable consequences such the ABO blood group polymorphisms. Glycosylation mutants in intact mice are even more uncommon. The rarity of such naturally occurring mutations could be explained in several ways. It is possible that they do occur frequently, but have little detectable biological consequence. A more likely possibility is that the great majority of them cause lethal aberrations that prevent completion of embryogenesis. A third possibility is that mutations in glycosylation remain undetected because of alternate or 'fail-safe' mechanisms that ensure that vital biological functions are carried out by more than one pathway. In this regard, it is worth noting that the congenital absence of a variety of highly conserved proteins in humans (e.g. glycophorin A, haptoglobin, prekallikrein, myeloperoxidase, coagulation factor XII and high molecular weight kininogen) are also known to have little biological or pathological consequence. Likewise, many 'knockout' experiments involving highly conserved proteins such as cellular proto-oncogenes have surprisingly limited consequences in the intact mouse (1047, 1049).

Creating mutants in glycosylation in intact organisms: a challenge for the future

To explore these issues, it appears necessary to create mutants in glycosylation in intact animals. Several possible approaches could be taken towards this goal. Antibodies or lectins specific for certain oligosaccharide sequences could be expressed in transgenic animals or injected into specific developing tissues. However, since such molecules are multivalent, they may

Table XIII. Altered oligosaccharides in diseases without a known primary defect in glycosylation

Glycoconjugate(s) affected	Change in oligosaccharides	Biological effect(s)	References
Plasma fibrinogen in hepatoma and in congenital dysfibrinogenaemias	Increased branching or number of *N*-linked oligosaccharides and increased sialic acid content	Prolonged thrombin time and reptilase time. Inhibition of coagulation	(278–280)
Plasma membrane and secreted proteins in cystic fibrosis	Generalized increase in fucosylation and sulphation	?Contribute to change in physical properties of secreted glycoproteins	(1013, 1014)
CD43 (leukosialin, sialophorin) in Wiskott–Aldrich syndrome	Altered branching of *O*-linked oligosaccharides	Decreased expression (due to altered glycosylation?)	(1015–1020)
Serum IgG immunoglobulin	Decreased galactosylation of *N*-linked oligosaccharides	A general feature of many chronic granulomatous diseases (rheumatoid arthritis, Crohn's disease, tuberculosis, etc.)	(34, 248, 254)
Several plasma proteins	Abnormal *N*-linked glycosylation of some glycoproteins. ?Primary or secondary defect in glycosylation	'Carbohydrate deficient glycoprotein syndrome'. Growth abnormalities, characteristic fat accumulations, abnormal electrophoretic mobility of certain serum glycoproteins, due to ?altered glycosylation	(1021–1032)
Dolichol oligosaccharides	Altered processing and accumulation of dolichol-linked mannosyl-oligosaccharides	Neuronal Ceroid-lipofuscinosis. ?Primary or secondary defect in humans, dogs and sheep	(1033–1036)

Note: unless otherwise stated, the defects reported in this table were found in humans.

disrupt development or other functions simply by causing unwanted cell–cell adhesion. Alternatively, the molecular cloning of glycosyltransferases allows overexpression, or the creation of 'knockout' mice lacking a specific sugar sequence. If such an intervention blocks early embryogenesis, the consequences may not be available for analysis (study of first-generation chimeric animals may give some information in gene-deletion experiments). However, even if live homozygous animals are observed with overexpression or with gene deletions, care must be taken in interpreting the results. The consequences seen could be the result of interference with other competing glycosylation pathways, or may be due to non-specific physical effects of grossly altered glycosylation in all tissues of the organism.

An alternate approach makes use of the fact that many microbial degradative enzymes are highly specific for certain outer sugar chain sequences. Thus, direct injection of specific endoneuraminidase into developing neural tissues yielded dramatic phenotypic changes (901, 905), suggesting specific roles for polysialic acids, and injection of heparanase into the developing embryo caused randomization of left–right axis formation (1048). Expression in transgenic mice of a viral sialic acid-specific 9-*O*-acetylesterase under the control of specific promoters caused abnormalities either early or late in development (940). In principle, the latter approach could be generalized to any situation where a cDNA is available encoding a specific oligosaccharide-degrading enzyme. Thus, rather than interfering with the basic genetic and cellular machinery responsible for the synthesis of specific oligosaccharides, one might eliminate them selectively after normal synthesis by expression of a degradative enzyme as a cell surface molecule. Specific promoters should limit expression of the enzyme and allow the analysis of tissue-specific functions of oligosaccharides in later stages of development, side-stepping an early lethal event that could have occurred with a gene 'knockout' experiment. In the short term, such approaches are likely to generate even more new questions than immediate answers. However, it is much better to have many incomplete clues to the biological roles of oligosaccharides than to have extensive and specific structural information only, and no way to pursue their relevance.

Future prospects

As recently suggested, modern progress in glycobiology 'has finally opened a crack in the door to one of the last great frontiers of biochemistry' (36). The future now appears bright for the understanding of many new biological roles of oligosaccharides. Until recently, mainstream research was focused either on the molecular biology of the single cell, or on the physiology of whole organs or organisms. In both of these disparate areas, the roles of oligosaccharides tend to be less prominent and can often be ignored or bypassed. However, the future of biology and biotechnology now lies in studies of cell–cell interactions, embryonic development, tissue organization and morphogenesis, and in the integration of these studies with the molecular physiology and pharmacology of organs and organisms. In these arenas, the biological roles of oligosaccharides seem to be critical and their understanding becomes crucial to further progress.

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Abbreviations

bFGF, basic fibroblast growth factor; CHO, Chinese hamster overy; EGF, epidermal growth factor; ER, endoplasmic reticulum; GM-CSF, granulocyte/macrophage colony-stimulating factor; HCG, human chorionic gondotrophin; HNK-1/L1, the antigenic epitope recognized by the HNK-1 antibody; I-CAM, intercellular adhesion molecule; LDL, low-density lipoprotein; LFA-1, leukocyte function antigen 1; MHC, major histocompatability complex; N-CAM, neural cell adhesion molecule; SSEA, stage-specific embryonic antigen; TGF, transforming growth factor.

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