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Special Invited Review

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Biological roles of glycans

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Abstract

Simple and complex carbohydrates (glycans) have long been known to play major metabolic, structural and physical roles in biological systems. Targeted microbial binding to host glycans has also been studied for decades. But such biological roles can only explain some of the remarkable complexity and organismal diversity of glycans in nature. Reviewing the subject about two decades ago, one could find very few clear-cut instances of glycan-recognition-specific biological roles of glycans that were of intrinsic value to the organism expressing them. In striking contrast there is now a profusion of examples, such that this updated review cannot be comprehensive. Instead, a historical overview is presented, broad principles outlined and a few examples cited, representing diverse types of roles, mediated by various glycan classes, in different evolutionary lineages. What remains unchanged is the fact that while all theories regarding biological roles of glycans are supported by compelling evidence, exceptions to each can be found. In retrospect, this is not surprising. Complex and diverse glycans appear to be ubiquitous to all cells in nature, and essential to all life forms. Thus, >3 billion years of evolution consistently generated organisms that use these molecules for many key biological roles, even while sometimes coopting them for minor functions. In this respect, glycans are no different from other major macromolecular building blocks of life (nucleic acids, proteins and lipids), simply more rapidly evolving and complex. It is time for the diverse functional roles of glycans to be fully incorporated into the mainstream of biological sciences.

Key words: biological roles, evolution, glycans

Introduction

In 1993, this journal published a review concluding that while lim ited evidence for all of the theories on the biological roles of glycans was available, exceptions to each could also be found (1). Some gen eral principles were suggested. First, the reported biological conse quences of experimental modification of glycosylation seemed highly variable, making it difficult to predict a priori the functions that a given glycan structure might be mediating, or its relative importance to the organism. Second, limited data suggested that the same glycan might mediate different functions at different locations within an organism, or at different times in its ontogeny. Third, the more spe cific intrinsic biological roles of glycans known at the time appeared to be mediated by unusual glycan sequences, unusual presentations of common sequences or further modifications of glycans. But it was also noted that such sequences were more likely to be targets for specific recognition by toxins and pathogenic microorganisms. It was therefore posited that ongoing host pathogen interactions might contribute to the evolution of some aspects of intra and inter species glycan variation. Finally, some suggestions were made as to how one might elucidate more intrinsic biological functions for gly cans. In particular, it was suggested that more studies of natural and induced mutations resulting in altered glycosylation within intact organisms would be required.

In the decade that followed, the author tracked several other more focused discussions of glycan functions, some examples of which are cited here (2 104). For a while it was indeed possible for an individual to track and read such reviews on biological roles of glycans, but this became increasingly difficult over time. By a decade

later it became impossible to do so, and one had to be content with tracking a sampling of reviews in areas of ongoing personal interest (105 159). Meanwhile, some of the concepts in the original review were updated in a book chapter (160). Evolutionary and phylogenetic perspectives on the matter have also since been extensively addressed (161 176). More recently, it has been emphasized that glycans are as universal in nature as nucleic acids, proteins, lipids and metabolites (177), and as essential to the existence of all known living organisms (178). But as depicted in Figure 1, glycans are also the most structurally diverse and rapidly evolving major class of molecules. Taken together with much greater technical difficulties in their analysis, one can understand why the knowledge base regarding these major building blocks of life has lagged so far behind.

Despite these challenges, it is evident that information regarding the biological roles of glycans has vastly expanded in the last two decades. The present review first surveys the history of how our understanding of biological roles of glycans originally evolved, and then attempts to update the overview as of mid 2016. As a measure of how much progress has been made, any attempt at being comprehensive is now impractical, and the knowledge base of a single individual cannot do justice to this vast and complex field. Thus, one is only able to illustrate general principles with a few selected examples, and with a strong emphasis on the expertise of the author. For the same reason, the bibliography of citations cannot be comprehensive. Also, most of the broad implications of glycosylation for biotherapeutics are not addressed (179).

It is assumed that the reader is generally familiar with the major types and classes of glycans found in nature, and the conventional terminologies for describing them (180). Of course, it is important to also recognize that the full range of types and distributions of glycans in nature are still largely unexplored, and surprises continue to emerge. To cite just a few examples, the following glycans were mostly unknown when the previous version of this review was being written: functional sialylation in the fly nervous system (181); *O* fucose and *O* glucose glycans on Notch (182 184), and *O* fucose on thrombospondin repeats (185); mucin type *O* glycosylation in protists (initiated with α GlcNAc instead of α GalNAc) (186); O linked *N* acetylglucosamine on cell surface/extracellular proteins (187 188); the C mannose linkage to proteins (189 190); the complexities of *O* mannose linked glycans in tissues such as muscle (191 194), including the novel glycosaminoglycan attached on α dystroglycan (195 200) generated by a dual function xylosyl/glucuronosyltransferase (201 204) and attached via novel ribitol phosphate bridge (205 208); a plant cell wall proteoglycan wherein a core arabinogalactan protein is glycosylated with cell wall matrix xylan and pectin glycans (209); identification of β galacturonic acid in a xyloglucan involved in plant root hair tip growth (210); the expanding diversity of milk oligosaccharides (211), recognition of immunomodulatory glycans in the gut microbiome (212 213); N linked glycans in prokaryotes (214 216) and, discovery of the large family of prokaryotic nonulosonic acids (217 219), the likely ancestors of sialic acids (220). The last two examples highlight the realization that many glycosylation types once thought to be unique to eukaryotes in fact have their origins in earlier evolved pathways in bacteria and archea (176, 221 222). In this regard, it is notable that many major taxa of life forms such as archea, fungi, protists and algae still remain poorly explored with regard to glycan structure and functions (many such taxa are not much addressed in this review).

Historical background

The first half of the 20th century saw great strides in elucidation of the structure and biochemistry of simple and complex glycans found in nature, garnering many Nobel Prizes (180). Beyond their well known roles in energy generation and metabolism, glycans obviously had many structural and biophysical roles in many systems, including nutritional storage. Given the dense coating of complex and diverse glycans on essentially all cell surfaces (sometimes called the "glycocalyx" in animal cells) as well as on most extracellular molecules, it was also not surprising to find many examples of infectious agents or symbiotic organisms that recognized such glycans with a high degree of specificity, mediating interactions with their hosts (223). Additionally many pathogens were found to express highly specific glycans on their own surfaces, which seemed to modulate their antigenicity and/or their susceptibility to bacteriophages. Meanwhile, pathogens were also found to elaborate highly specific exo and endoglycosidases that could degrade host glycans. In fact, many of the structural details of eukaryotic glycans were initially deduced by using such microbial glycosidases as tools (224 226).

The discovery of corresponding lysosomal glycosidases intrinsic to eukaryotic systems (227) then led to a better understanding of so called "storage disorders", wherein the deficiency of a single lysosomal glycosidase resulted in accumulation of the corresponding nondegraded product in lysosomes (228). Meanwhile, great strides were made in elucidating the structures of glycans in some taxa

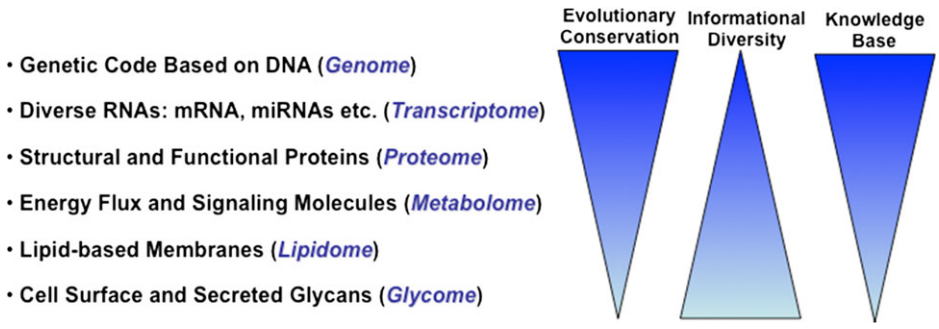

Fig. 1. Universal characteristics of all living cells. As indicated in the figure and discussed in the text, glycosylation is among the key features of all living cells. However, in contrast to the genetic code, the degree of chemical complexity and evolutionary diversification of glycans amongst various taxa is the greatest. The likely reasons for this difference are discussed in the text, and can help explain the still rather limited knowledge base regarding this class of molecules. But we now know that dense and complex glycosylation is universal to all living cells and even most viruses. Evidently, more than 3 billion years of evolution has failed to generate a free-living cell devoid of glycosylation. Thus, one can conclude that glycosylation is as essential to life as a genetic code. Figure modified from ref. 178 and used with permission from Varki A. 2011a. *Cold Spring Harb Perspect Biol. 3*, doi:pii: 10.1101/cshperspect. a005462. Copyright: Cold Spring Harbor Laboratory Press.

(particularly vertebrates), as well in understanding their biosynthetic pathways. The development of vertebrate cell lines with defined defects in most glycosylation pathways provided powerful and con clusive evidence for many complex glycan biosynthetic pathways, and tools for their in depth study (229 240), especially N linked glycans on glycoproteins. Ironically, in vitro viability of these remarkable cell lines despite their gross defects in glycosylation raised questions in the minds of some scientists, as to whether com plex glycans have specific and critically important functions intrinsic to intact vertebrate organisms.

Despite all these great strides in understanding the structure, bio synthesis and metabolism of glycans in several taxa, remarkably little was still known about their specific functions, beyond their metabolic, structural, biophysical and pathogen facilitating roles. But early clues did exist for more specific intrinsic biological roles. Some of the "blood groups" that limited blood transfusion between individual humans could be explained by intraspecies variations in glycosylation (241). The effects of glycosidase pretreatment on the subsequent intra vascular trafficking of blood cells in vivo raised the possibility that gly cans might serve as targeting signals (242). The role of mammalian α lactalbumin in the generation of lactose in milk had also been eluci dated (243), but the functional relevance of the resulting profusion of species specific milk oligosaccharides elaborated from a lactose core oligosaccharide (244) remained elusive. A consistent finding of altered glycosylation in malignant cells suggested specific roles in cancer pro gression (245 247). The selective reaggregation of dispersed sponge cells was shown to be due to carbohydrate carbohydrate interactions between large acidic glycans (248).

Meanwhile, a major clue to a specific role of glycans in verte brate systems emerged with the discovery of the asialoglycoprotein receptor, which recognized and bound to exposed β linked galactose residues on desialylated glycoproteins, to rapidly clear them away in the liver (249 250). But the intrinsic biological function of this highly specific hepatocyte endocytic receptor remained obscure at the time. Regardless, the concept that a terminal sugar on a glycan could act as an intraorganismal targeting signal was established, and evidence then emerged for a mannose receptor on macrophages (251 252) and possibly one for mannose 6 phosphate on other cell types (253 254). The isolation and characterization of many plant and animal glycan binding proteins by methods such as affinity chromatography occurred in parallel (255 263). During this period, the well known pharmacological anticoagulant effect of the natural glycosaminoglycan heparin was shown to be due to a highly specific interaction of antithrombin with a particular 3 *O* sulfated sequence (264 266) within the heparin chain. These and other such findings provided *indirect* evidence that complex glycans might carry out specific functions of intrinsic value to the complex multicellular organisms that synthesized them. However, as of the end of the 1970s there remained *no direct proof* that glycans played such key biological roles. Even as late as 1988, the introduction to a major symposium on the topic stated that "...while the functions of DNA and proteins are generally known...it is much less clear what carbo hydrates do..." (267).

In reality, a few specific examples had been defined earlier in the 1980s. The discovery and characterization of the rare human genetic disorder called I cell disease (268) had led to the prediction that lysosomal enzymes shared a common recognition marker that mediated organelle specific uptake into cells (269). The blockade of this uptake by mannose 6 phosphate (but not glucose 6 phosphate) (253) then led to the correct prediction that the glycans on these enzymes must selectively express a novel phosphomannosyl marker (254, 270) that was recognized by specific receptors, which might mediate both intra and intercellular trafficking of these enzymes to their correct destination in lysosomes.

Elucidation of the biological significance of this presumed lyso somal enzyme trafficking pathway required the determination of the structures of the novel glycans involved (271 273), and discovery of the enzymatic basis of the generation of this "phosphomannosyl rec ognition marker" (274 281). All of this work culminated in the dis covery of the biochemical defect in I cell disease and related human genetic disorders, which turned out to be a failure of the initial phos phorylation mechanism (276 278). Thus, for the first time one could state that specific recognition of a unique glycan mediated an equally specific and critical biological role, which was of intrinsic value to the organism that had synthesized the glycan.

A few years later, studies showed that small fungal cell wall gly can fragments could send highly specific signals to plants. Signal transmission depended on the precise stereochemistry of the glycans (282 284). This concept of "oligosaccharins" was extended to other glycan fragments that could manipulate morphogenetic pathways of tobacco explants (285) providing preliminary evidence that glycans by themselves might act as signaling molecules internal to a species. Meanwhile, studies in animals indicated that sialidase treatment could abrogate the interaction of lymphocytes with high endothelial venules in lymph nodes (286) leading to the correct prediction that sialylated glycan signals were involved in the trafficking of lympho cytes out of the circulation. Along with other convergent lines of evi dence, this eventually resulted in the definition of a family of cell adhesion molecules (287 288) that were critical for leukocyte roll ing on endothelium, prior to their exit from the circulation. These molecules were called "selectins" (289), and they recognized a com mon motif, consisting of sialylated fucosylated glycans (7, 13, 24, 91, 103, 128, 140, 290 309); a topic that has continued to blossom, with implications for many fields.

While all this progress was occurring, it was generally assumed that glycosylation was only found on cell surface and secreted mole cules, and that the nucleus and cytoplasm were devoid of this class of post translational modification. The discovery of O linked GlcNAc (310 314) thus went unrecognized even by most other gly coscientists for years, until it was finally realized that this nucleocy toplasmic modification is the most common form of glycosylation in eukaryotic cells (314 316), and that it mediates numerous modula tory functions on many proteins, including a complex interplay with protein phosphorylation (317 320).

The increasing number of animal lectins that being discovered and characterized was then classified based on sequence homologies into C type and S type lectins (321), and the latter were eventually redesignated as galectins (322 323). Discovery of the sialic acid binding properties of sialoadhesin (324) and of CD22 (325), fol lowed by the cloning of sialoadhesin (326), led to the definition of a new family of cell type specific vertebrate lectins initially called "sia loadhesins" (15, 327), but eventually designated as a subfamily of I type lectins (328) and renamed as the Siglecs (329). The previously discovered phosphomannosyl receptors were now redesignated as "P type" Lectins (85) and some previously known plant lectins became founding members of the "R type" (Ricin like) and "L type" (Legume lectin like) families (330). The power of phyloge nomic sequence comparisons has since revealed many additional families of lectins such as the X type lectins (intelectins) (331 333), Ficolins (334 335), etc. The earlier mentioned somatic cell mutants in pathways of *N* and *O* glycosylation played key roles in this pro gress. Along with the discovery of new human genetic disorders in

glycosylation (see next section), these and many other clues to intrinsic biological roles of glycans in the 1990s finally opened up this vast and uncharted territory of biology. Combined with the accelerating power of genomics and glycomics, we have now reached a point where numerous biological roles of glycans have been elucidated, to varying degrees of precision. For reasons of brevity, only a few examples are considered in this review.

Learning from natural or induced genetic alterations of glycosylation in multicellular organisms

Many different approaches have been used to elucidate the biological roles of glycans. Among these, one of the most instructive has been the study of genetic alterations of glycosylation in model organisms, and in human diseases. Indeed as mentioned earlier, it was the discovery of the genetic defect in I cell disease that conclusively proved the biological significance and importance of the mannose 6 phosphate targeting pathway in vivo. At about the same time a defect in 3′ phosphoadenosine 5′ phosphosulfate (PAPS) formation was found in brachymorphic mice with multiple sulfation defects. While PAPS has many roles, the disproportionately short stature of the mice was apparently due to undersulfation of chondroitin sulfate in epiphyseal growth plate cartilages (336). Another decade went by (see Figure 2) before the second human biosynthetic defect specific to glycosylation was discovered, a deficiency of a glycosaminoglycan core galactosyltransferase in a progeria like syndrome (337). Meanwhile, the concept of "Carbohydrate Deficient Glycoprotein syndromes" (CDGs) had been suggested, based on the finding that children with previously unexplained multisystem disorders showed under glycosylation of serum transferrin (338 341) a test originally devised to detect alcoholism via the general hyposialylation it causes in liver derived serum glycoproteins (342)! The work of many investigators then led to the elucidation of the underlying enzymatic and genetic defects in these children (343 350), eventually resulting in the repurposing of the acronym CDG to denote "Congenital Disorders of Glycosylation" (66, 351 356). After a slow start in the early 1990s an international effort of many investigators has now resulted in a veritable explosion in discoveries of human genetic disorders of glycosylation (Figure 2) (61, 67, 191, 352, 357 382). These disorders continue to provide a goldmine of clues to biological roles of glycans, and this understanding has begun to benefit some patients via simple monosaccharide replacement therapies (374, 383 388). Notably, in a recent study of

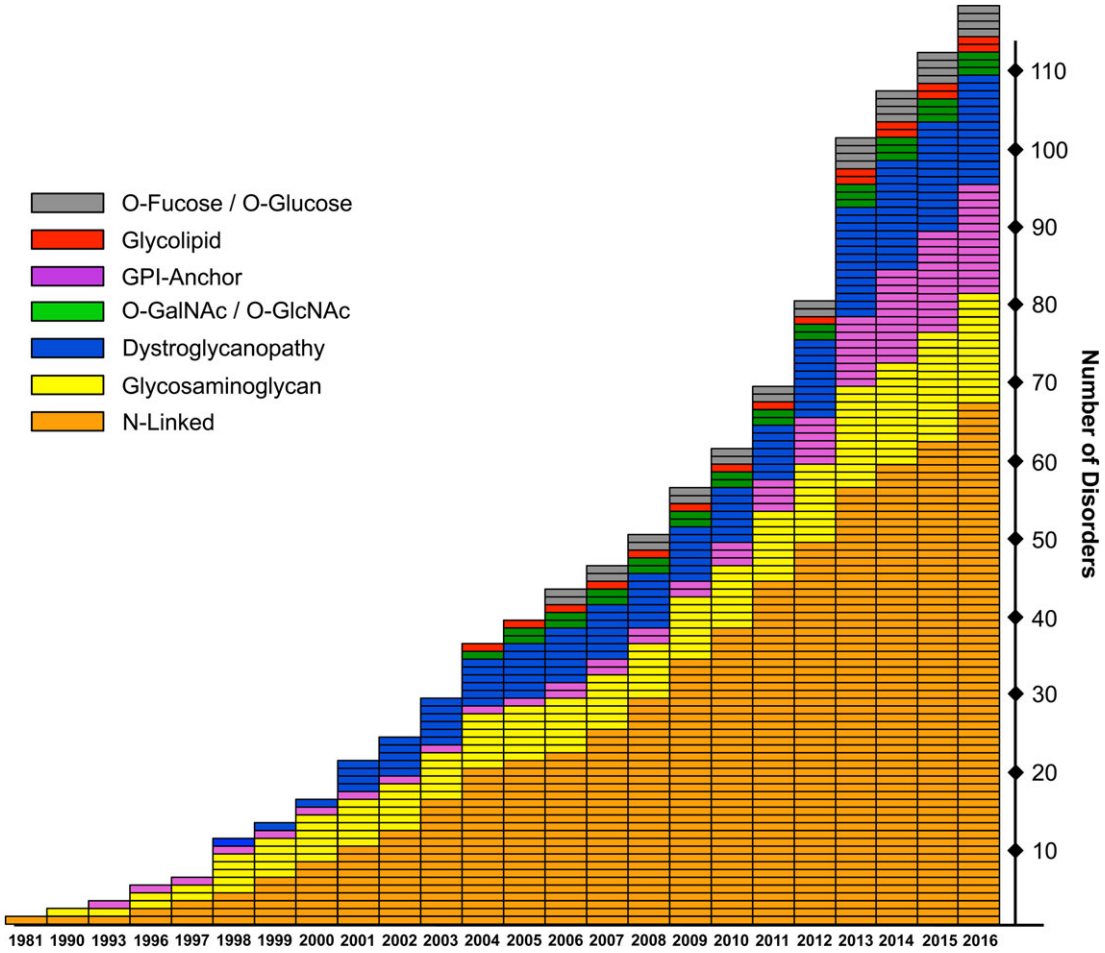

Fig. 2. Accelerating progress in the discovery of human glycosylation disorders. The graph shows the cumulative number of human disorders with a major genetic defect in various glycosylation pathways and the year of their identification (2016 data for first 6 months). In early years, initial discovery was based on compelling biochemical evidence, and in later years by conclusive genetic proof. In most instances, the year indicates the occurrence of definitive proof of gene-specific mutations and correlations to biochemical results. Figure kindly provided by H. Freeze and Bobby Ng, updated from ref. 375 and reproduced with permission from Freeze HH, Chong JX, Bamshad MJ, Ng BG. 2014. *Am J Hum Genet*. 94:161 175. Copyright Elsevier. Reproduced with permission.

consecutively enrolled patients with unexplained intellectual devel opmental disorder and metabolic phenotypes, whole exome sequen cing showed that >10% were attributable to genetic defects in glycosylation pathways (389), mostly hypomorphic states of genes in which complete loss would have been lethal.

Beyond the clinically obvious CDGs, there is also increasing gen etic evidence for the role of glycosylation related genes in more sub tle and common diseases in the population, as observed in genome wide association studies a few examples of which are mentioned here: *NDST3* (390) and *ST8SIA2* (391 393) in schizophrenia and bipolar disorder; *FUT2* nonsecretor status and blood group B asso ciated with elevated serum lipase activity and risk for chronic pan creatitis (394); and type 2 diabetes susceptibility associated with *ST6GAL1* (395).

Meanwhile, targeted genetic alterations of glycan biosynthetic pathways in mice (396 401) also revealed a spectrum of abnormal ities, again pointing to complex and varied functions of glycans in multicellular organisms. Since then, the list of mice with genetically altered glycosylation has expanded greatly, and resulting phenotypes have been highly instructive (98, 159). It is ironic that most of the glycosylation pathways that had earlier been dismissed because gen etic defects caused "limited phenotypes" in the reductionist environ ment of the tissue culture dish later turned out to have clear and serious consequences in the intact organism, even in the form of hypomorphic alleles in humans. On the other hand, the phenotypic outcome of gene knockouts has been rather unpredictable. For example, while the MGAT1/GnT I null state (which prevents the processing of *N* glycans) caused embryonic lethality in mice (397 398), it generated no grossly obvious phenotype in the *Arabidopsis* plant (402 403), and limited phenotypes in *Drosophila* (404). Conversely while mice lacking ST3GAL5 seem to have only moder ate phenotypes (405 406), humans with similar defects suffer from severe multisystem disease (407 408). Of course, any report of a "viable and fertile mouse with *no major* phenotype" must be taken with a large grain of salt. For example, the consequences of altering complex ganglioside biosynthesis (409 411) or of knocking out one of the key ganglioside receptors called MAG (412 413) was mostly evident later in the life, or when the mouse was subjected to specific challenges (414 415). In contrast, complete elimination of ganglio side biosynthesis gave an early embryonic lethal phenotype (416). Further complexity has arisen from the realization that there are mul tiple isozymes of some glycosyltransferases (417 418), and that post transcriptional regulation by micro RNAs is occurring (419 420).

Summaries of all human and model organism phenotypes resulting from genetic alterations in glycosylation will not be attempted here, and are reviewed elsewhere (98, 159, 375, 378). In general, complete elimination of major classes or subclasses of glycans tends to result in embryonic lethality, while defects in outer terminal structures often give viable organisms with defects in specific functions and/or specific cell types, although these impacts are often species specific. As an example, null alleles preventing the synthesis of the core glycosamino glycan backbone of heparan sulfate causes embryonic lethality (421 422), but the prevention of proper sulfation of this backbone can give living mice with specific defects (422 427). When embryonic lethality makes it difficult to define specific biological roles, tissue specific tar geted genetic alterations became important (428 430). Experiments of nature such as somatic mutations in X linked genes (431) and hypo morphic alleles of essential genes (388 389, 432) have also helped our understanding of functions.

Note that the discussion above largely focused on examples from animals. While space does not allow a detailed discussion, loss of glycosylation in plants, fungi or prokaryotes can also lead to cell death. For example, a meristem localized inducible expression of an UDP glycosyltransferase gene is essential for growth and develop ment in pea and alfalfa (433). Ethambutol (a traditional drug treatment for tuberculosis) is now known to target the arabinofura nosyltransferases EmbA and EmbB (434). Knockouts of these genes in mycobacteria are lethal, as is the case with some other glycosyl transferases (435). And in the fungus *Aspergillus fumigatus*, inhib ition of cell wall β glucan synthesis is toxic (436 437).

A broad classification of the biological roles of glycans

There are several different ways to classify the biological roles of gly cans, based on the glycan types in question, on the glycan binding pro tein involved, etc. A simple and broad classification (160) (see Figure 3 for a conceptual organization and Table I for a complete listing) divides glycan functions into four somewhat distinct categories. The first is structural and modulatory roles (including nutrient sequestra tion). The second category involves extrinsic (interspecies) recognition. The third is intrinsic (intraspecies) recognition. Finally, there is molecular mimicry of host glycans. All of these categories can involve glycan binding proteins (see Figure 3). The next part of this review considers these classes of biological roles and discusses one or more examples of each. Given the vastness of relevant literature, the exam ples and citations are rather limited and biased towards the knowledge of the author. Examples of multifunctional roles of glycans and glycan binding proteins that cross over between these somewhat arbi trary categories will be mentioned later.

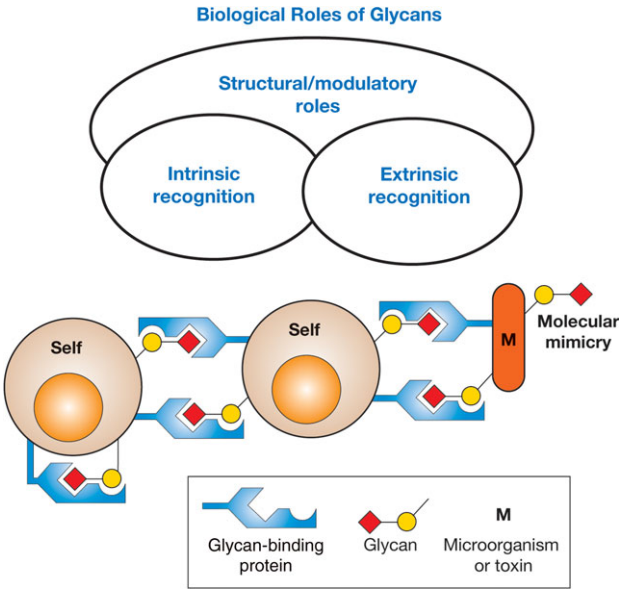

Fig. 3. General classification of the biological roles of glycans. A simplified and broad classification is presented, especially emphasizing the roles of organism-intrinsic and organism-extrinsic glycan-binding proteins in recog nizing glycans. There is some overlap between the categories, e.g., some structural properties involve specific recognition of glycans. Binding shown on the left of the central "self" cell represents intrinsic recognition, and extrinsic recognition is represented by binding shown to the right of that cell. Molecular mimicry of host glycans adds further complexity to potential roles. Original drawing by R. Cummings, updated from ref. 160 with permis sion from the Consortium of Glycobiology Editors.

Table I. Biological roles of glycans

Structural and modulatory roles
Physical structure
Physical protection and tissue elasticity
Water solubility of macromolecules
Lubrication
Physical expulsion of pathogens
Diffusion barriers
Glycoprotein folding
Protection from proteases
Modulation of membrane receptor signaling
Membrane organization
Modulation of transmembrane receptor spatial organization and function
Antiadhesive action
Depot functions
Nutritional storage
Gradient generation
Extracellular matrix organization
Protection from immune recognition
Effects of glycan branching on glycoprotein function
Cell surface glycan:lectin based lattices
Masking or modification of ligands for glycan binding proteins
Tuning a range of function
Molecular functional switching
Epigenetic histone modifications

Extrinsic (interspecies) recognition of glycans
Bacterial, fungal and parasite adhesins
Viral agglutinins
Bacterial and plant toxins
Soluble host proteins that recognize pathogens
Pathogen glycosidases
Host decoys
Herd immunity
Pathogen associated molecular patterns
Immune modulation of host by symbiont/parasite
Antigen recognition, uptake and processing
Bacteriophage recognition of glycan targets

Intrinsic (intraspecies) recognition of glycans
Intracellular glycoprotein folding and degradation
Intracellular glycoprotein trafficking
Triggering of endocytosis and phagocytosis
Intercellular signaling
Intercellular adhesion
Cell matrix interactions
Fertilization and reproduction
Clearance of damaged glycoconjugates and cells
Glycans as clearance receptors
Danger associated molecular patterns
Self associated molecular patterns
Antigenic epitopes
Xeno autoantigens

Molecular mimicry of host glycans
Convergent evolution of host like glycans
Appropriation of host glycans

Structural and modulatory roles

Given their ubiquitous presence and abundance in all cellular compartments, extracellular spaces and body fluids, glycans have many major biological effects mediated by their own primary structural properties, and/or by modulating functions of proteins and lipids to which they are attached. The randomly selected examples provided in each section do not focus on any particular glycan class per se.

Physical structure

β Linked homopolymers of glucose or *N* acetylglucosamine (cellulose or chitin, respectively) are among the most abundant organic molecules on the planet, providing strength and rigidity to structures such as plant and fungal cell walls and arthropod exoskeletons (438 439). These polymers are also difficult to breakdown by physical, chemical or enzymatic means. Many other glycan polymers play major roles in fungal and plant cell wall structure and function (438 447). For example, the hemicellulose xyloglucan not only plays a key role in the loosening and tightening of cellulose microfibrils, but also enables the plant cell to change its shape during growth and differentiation, and to retain its final shape after maturation (441). Needless to say, in the absence of these and many other major glycan polymers, the diversity of macroscopic structural variations in life forms on the planet would be far more limited.

Physical protection and tissue elasticity

There are many instances where thick layers of glycans provide an important physical protective role. In addition to the polymers mentioned above, the dense layer of mucins that coats many epithelial surfaces such as the inner lining of airways and intestines provides critical barrier functions, including protection against the invasion by microorganisms that live within the lumen (139, 418, 448 452). Disruption of this layer by genetically altering mucin backbones, O linked glycosyltransferases (or key chaperones like *Cosmc*) can have very serious consequences, including inflammation and carcinogenesis associated with microbial invasion (453 456). Likewise the thick and biochemically robust cell walls of plants make it difficult for invading fungi and bacteria to reach the membrane of the plant cells (438, 441, 444, 446 447). In other instances, the thick layer of glycans also provides tissue strength. Nature is rife with many more such examples including fungal and bacterial cell walls and polysaccharide coats, and the glycosaminoglycans of vertebrate cartilage, which are partly responsible for its elasticity, resiliency and compressibility (457).

Water solubility of macromolecules

It is interesting that many vertebrate internal body fluids such as blood plasma are rich in heavily glycosylated proteins. Apart from specific functional reasons for glycosylation, hydrophilic and acidic glycans also contribute significantly to the water solubility of these macromolecules. Indeed the remarkably high concentration of proteins in the blood plasma (~50 70 mg/mL in humans, carrying ~2 mM of bound sialic acids) would probably be impossible without this glycosylation. The antifreeze glycoproteins of certain fish alter the structure of bulk water itself, preventing nucleation of ice crystals in body fluids (458 461). Antifreeze functions can also be mediated by certain polysaccharides with a lipid component (460).

Lubrication

The remarkably efficient lubrication provided by soluble and membrane bound mucins on the lining of hollow organs may seem like a trivial "function" until one realizes that deficiencies in oral salivary mucins caused by radiation damage to salivary glands (a side effect of head and neck cancer treatment) (462 463) or by autoimmune disease (Sjogren's) (464) can be life threatening, especially by limiting the ability to swallow food. Another example is the critical lubricating role of hyaluronan in body fluids (465 467),

such as the synovial fluid in joint cavities and tear fluid in the eyes, wherein deficiencies can be supplemented therapeutically (467 471).

Physical expulsion of pathogens

Heavily glycosylated secretions produced in large amounts can serve as a response to physically expel intruders. For example, expulsion of *N. brasiliensis* worms from the rat intestine is associated not only with quantitative, but also with qualitative changes in the composition of mucins in goblet cells (472). On the microscopic level, a recent study shows that a "sentinel" goblet cell localized to the mouse colonic crypt entrance recognizes bacterial products, activating the Nlrp6 inflammasome, eventually inducing mucin secretion from adjacent goblet cells in the upper crypt, which expels bacterial intruders that have penetrated the protective inner mucus layer (473).

Diffusion barriers

Extracellular matrix glycosaminoglycans and/or heavily sialylated glycoproteins can comprise critical diffusion barriers. For example, the heavily sialylated protein podocalyxin on glomerular podocyte foot processes (474 478) and heparan sulfate glycosaminoglycans within the glomerular basement membrane (479 484) seem to play important roles in maintaining the integrity of blood plasma filtration by the kidney. Pathological or experimental damage to such glycans causes large molecules like albumin to escape into the urine, and is associated with glomerular diseases (478, 485 491).

Glycoprotein folding

Protein molecules that are synthesized and secreted via the ER Golgi pathway can be subjected to ER modifications such as *O* fucosylation (492) and *O* mannosylation (493), with important effects on facilitating proper folding in the ER lumen. A major fraction of such ER synthesized proteins are also modified by N linked glycans at Asn X Ser/Thr sequons (494), and it is reasonable to think that the large, generally hydrophilic sugar chains contribute to proper folding of nascent polypeptides emerging into the lumen of the ER. Indeed, it has long been known that preventing N linked glycosylation using the inhibitor tunicamycin can have negative effects on the initial folding of such proteins (495 496). In keeping with the highly conserved structure of the initial glycan added to asparagine residues, we now know that such *N* glycans play a much more precise role in actually directing the folding, via specific recognition of certain features of *N* glycans (see further discussion on quality control below). Even at the level of initial protein folding the exact context of the sequon can dictate the outcome. For example, experimentally placing a phenylalanine residue two or three positions before a glycosylated asparagine in distinct reverse turns facilitates stabilizing interactions between the aromatic side chain and the first GlcNAc residue of the glycan, while increasing glycosylation efficiency (497).

In this context, it is worth noting that the vast majority of published crystal structures of naturally occurring glycoproteins are derived from proteins that either had their glycosylation sites mutated, or had their glycans partially or completely degraded, prior to crystallization. The practical reason for making such a drastic change is that glycans are often heterogeneous and have a high range of motion, making it difficult to obtain an ordered crystal. Even if crystallization is possible, the glycans are typically disordered within the resulting image. In instances where glycans are left intact, the glycoproteins are often expressed in heterologous cells, resulting in nonspecies specific glycosylation. This major technical artifact is rarely addressed in prominent protein crystallography papers. The bottom line is that when glycosylation sites are mutated or glycosylation is modified, there is a significant possibility that the folded form defined by crystallography may not be the native state. Solving this technical problem remains a major challenge for the future (498 500), one in which new techniques such as cryo electron microscopy (501 502) may help. Meanwhile, it is definitely a worthwhile exercise to model the glycans back into the crystal structure to a best approximation (501, 503). Exceptions to the general lack of glycans in crystal structures can occur when the glycan is buried and partially immobilized within the folds of the protein, such as in the case of the Immunoglobulin G (IgG) Fc region (504 506), or tightly packed on the surface, such as in the HIV virion (507 509).

Protection from proteases

Heavily glycosylated proteins are protected from protease cleavage by glycans, likely by steric hindrance or negative charge. This effect is particularly prominent for mucins carrying densely packed *O* glycans (451, 510). Indeed, extended segments of some mucins are even resistant to broad spectrum proteases like proteinase K (511 512). This property can actually be taken advantage of, to isolate mucin segments away from other proteins that could be more easily proteolyzed into smaller fragments, or even from whole tissues (511 512). In a prokaryotic example, N glycosylation in Campylobacter improves fitness, by providing protection against proteases in the gut (513). Conversely, there is evidence that glycosylation at single sites can regulate specific cleavage events with large impacts on protein activity (514), e.g., the protection of Tango1 by O glycosylation is critical to apical secretion in Drosophila (515).

Modulation of membrane receptor signaling

Classic studies have shown that glycolipids can alter the signaling properties of protein receptors present within the same cell membrane (516). For example, subtly different forms of the sialylated ganglioside GM3 can have differential effects on tyrosine kinase signaling of the EGF receptor (517 522) and elimination of GM3 affects insulin receptor action (405, 523 524). Another classic example is the co receptor activity of heparan sulfate in FGF signaling (525 526). Glycosylation can also affect the signaling properties of the proteins to which it is attached. For example, α1 6 core fucosylation of *N* glycans affects transforming growth factor (TGF) signaling (527). Dysregulation of TGF β1 receptor activation leads to abnormal lung development. While most core fucose deficient mice die 3 d after birth, the survivors develop emphysematous changes of the lung. The underlying mechanism appears to be dysregulation of downstream TGF signaling, causing MMP gene activation, which eventually degrades alveolar membranes to give emphysema. In a similar vein, both sialylation and fucosylation modulate epidermal growth factor receptor mediated intracellular signaling (528 530).

An entirely new field opened up with the discovery that the Fringe molecule is a glycosyltransferase that modifies the important signaling protein Notch and thus modulates Notch Delta interactions (182, 184). Before Fringe can act, Notch must first be glycosylated with an *O* fucose, and the protein *O* fucosyltransferase 1 is thus an essential component of Notch signaling pathways (531 532). It was later discovered that the *O* glucose modification on Notch added by a glucosyltransferase encoded by Rumi is also essential for Notch signaling and embryonic development (533 534). Thus there are many roles of glycosylation in Notch signaling (535 536). The structural basis of glycosylation mediated

Notch interactions with some of its ligands has been recently explored (537).

Membrane organization

Glycans can have profound effects on the organization of cell membranes. For example, GPI anchored proteins are mainly associated with glycolipid enriched membrane microdomains (538) and are organized in submicron domains at the cell surface (539). Cell surface lectins may also participate. Galectin 4 appears to be the major organizing factor of such "lipid rafts" on gastric epithelial cells (540). GPI anchored proteins are selectively targeted to the apical surface in fully polarized epithelial cells (541). It also stands to reason that the glycans on cell surface glycoproteins can modulate membrane domain organization by their bulk and charge (542 543). It now appears that glycans on one class of glycoproteins can even modulate the organization of other classes of glycans on other proteins present on the same cell surface, perhaps forming "clustered saccharide patches" (146, 302, 544). The formation of galectin mediated lattices in the glycocalyx is discussed below.

Modulation of transmembrane receptor spatial organization and function

In addition to the role of heparan sulfate proteoglycans in modulating transmembrane receptor spatial organization discussed above, bulky glycoproteins in the cell surface glycocalyx can indirectly promote cell adhesion and signaling, facilitating integrin clustering by funneling active integrins into adhesions and altering their state, by applying tension to these matrix bound molecules (545). This in turn promotes focal adhesion assembly and facilitates integrin dependent growth factor signaling to support cell growth and survival. Since a bulky glycocalyx is a feature of malignant cells, it is suggested that these features could foster the spread of cancer by mechanically enhancing cell surface receptor function (545). However such mechanisms are also likely to operate in normal cells, which presumably exist in a continuum of biophysical states of the glycocalyx.

Antiadhesive action

Large acidic polymers such as hyaluronan and polysialic acid can inhibit cell cell and cell matrix interactions by virtue of both bulk and negative charge. These antiadhesive functions are particularly prominent during phases of development when cell migration is very active. The "plasticity" resulting from polysialic acid expression appears to be important for neuronal migration as well as reorganization following injury (546 554).

Depot functions

Hydrophilic glycans on cell surfaces and extracellular matrices are capable of attracting and ordering water molecules (555). Beyond retaining water and cations (for unknown reasons, positively charged glycans are uncommon in nature), extracellular matrix glycosaminoglycans and polysialic acid can act as depots for growth factors and other bioactive molecules, which can be stored locally and released when needed, e.g., during injury and wound healing (86, 556 561).

Nutritional storage

Polymeric glycans like glycogen in animal cells and starch in plants serve obvious roles in the long term storage of glucose as an energy source, and marathon runners must build up liver glycogen stores before the big race. The earlier comment about O linked GlcNAc being the first known form of cytosolic glycosylation is not strictly true, as the glycogenin protein was also known to self glucosylate itself on a tyrosine residue with a short 8 12 glucose residue polymer in order to serve as the primer for glycogen synthesis (562 567). In contrast, the mechanism of potato starch biosynthesis appeared to involve de novo synthesis, not an amylogenin primer (568).

Gradient generation

Gradients of growth factors can be generated by binding to extracellular matrix glycosaminoglycans such as heparan sulfate, especially in embryonic development (86). This organization of growth factors by glycosaminoglycans may contribute the morphogen gradients that are critical during development (569 572).

Extracellular matrix organization

Many components of the extracellular matrix in vertebrates are large glycan polymers such as sulfated glycosaminoglycans and hyaluronan, that self organize along with specific proteins into larger aggregates to generate structures such as basement membranes (573 574) and cartilage (575 577). Cartilage also acts as a template for primary and secondary ossification centers, development of the growth plates and the end of long bones, and the laying down of bone (578). Organizational roles are also obvious for glycans in the extracellular matrices of plants (see discussion above), and new roles are emerging for glycans in the biofilms surrounding bacteria, enabling them to form discrete multicellular communities (579 583).

Protection from immune recognition

The adaptive immune system of vertebrate organisms functions largely by recognition of foreign peptide sequences, which are directly recognized by the B cell surface Ig receptor (584 585), and are also loaded into the grooves of the major histocompatibility receptors to be presented to specific T cell receptors (586). If the peptide carries a very small glycan, this moiety can contribute novel specificity to recognition (587 591). However larger glycans typically disrupt peptide loading and/or T cell receptor recognition, and often eliminate it altogether. This explains a common immune escape strategy of enveloped viruses, whose surface glycoproteins tend to be very heavily glycosylated (592 593). Sometimes, such protective glycosylation can become so dense that it generates unique clustered epitopes recognized by specific antibodies, such as that seen on the surface of the HIV virion (507 509, 594). In other instances, one type of glycan can block immune recognition of another, such as the *Cryptococcus neoformans* yeast cell wall, which is required for virulence (595 596), apparently by protecting the deeper structures of the organism from recognition and attack by the host immune system.

Effects of glycan branching on glycoprotein function

The N linked glycans on cell surface glycoproteins can have varying degrees of branching (597), and glycan branching is specifically upregulated in T cell activation (598), and in malignant transformation (599 604). Beyond their effects on protein structure per se, certain branched glycans can affect a variety of biological functions. Thus, there are reports of regulation of cytokine receptors by modulation of endocytosis rates by the type of glycan structure and branching (605), and *N* glycan number and degree of branching can cooperate to regulate cell proliferation and differentiation (606) as

well as thymocyte positive selection (607). The degree of branching of *N* glycans is primarily dependent on the addition of β linked GlcNAc residues donated by UDP GlcNAc. Given that glucosamine and GlcNAc are major metabolic intermediates in most cells, the level of UDP GlcNAc provides a likely connection between cellular metabolism, cell surface organization and disease (608). In keeping with this concept, the cell surface residency time of glucose transporter 2 is regulated by branching of its *N* glycans, and alters insulin secretion as well (609). This provides a connection between diabetes, pancreatic β cell glycosylation and glucose transport (610). A different kind of *N* glycan branching (so called bissecting GlcNAc) inhibits growth factor signaling and retards mammary tumor progression (611) and E cadherin may be a target molecule for this glycan modulating effect (612 613).

Cell surface glycan:lectin-based lattices

The glycocalyx on the surface of vertebrate cells is often likened to a semi randomly organized tropical rain forest (146), or to a sea floor kelp bed (the latter analogy by P. Gagneux adds water and motion to the image, making it even more realistic). But the glycocalyx is also suggested to include self organizing ordered lattices of glycans and lectins (83, 614 615). An intriguing connection has been established between the glycan branching phenomena mentioned above and the formation of such cell surface lattices involving galectin recognition of polylactosaminoglycans, which tend to be enriched on highly branched glycans (117, 606, 608, 616). The concept is that an ordered lattice forms within the glycocalyx that alters interactions between cell surface molecules, also affecting their rates of clearance from the cell surface by endocytosis. Thus, evolutionary selection is suggested to have modulated the number of glycans of inhibitory versus activating growth factor receptors, such that branching (controlled by UDP GlcNAc and GlcNAc transferases) can differentially affect their relative ratio on the cell surface, by altering cell surface residence times (606, 608, 616 617). Complexity arises because capping of polylactosaminoglycans by sialic acids can modulate galectin recognition by its presence and or linkage type (618 622).

Masking or modification of ligands for glycan-binding proteins

In some cases, modifications of monosaccharides and/or specific monosaccharides themselves can act as biological masks that prevent the recognition of the underlying glycan by specific glycan binding proteins (623). Classic examples can be found in the case of terminal sialic acid wherein *O* acetyl modifications can block the binding of some influenza viruses (22, 623 624), and the removal of sialic acid itself can unmask binding sites for receptors or antibodies that recognize subterminal β galactose residues (22, 623). In another example, certain enzymes called Sulfs mediate extracellular removal of binding sites for heparin sulfate ligands (625), which can then signal through other receptors, e.g., wnt/frizzled or IFN β/IFNAR (626 628).

Tuning a range of function

The size, number, branching and degree of sialylation of *N* glycans can generate numerous glycoforms of a single polypeptide such as erythropoietin (629 640) or GM CSF (641 644). It turns out that the nature of the glycosylation, extent of branching and level of sialylation modulate the activity of such cytokines over a range of function, by affecting its interaction with its cognate receptor, and also by altering the rate of clearance from the circulation. In passing, it is worth mentioning that differences in the sulfation and sialylation of the *N* glycans expressed on endogenous versus exogenous erythropoietin are used by the Anti Doping Agency to detect illicit administration, and has led to rescinding of many major sporting trophies (645 646).

Molecular functional switching

The once obscure (310), but now well known and widespread, O GlcNAc modification of nuclear and cytoplasmic proteins, has been shown to be a multifunctional molecular switch, which can work with, or in competition against, Ser/Thr phosphorylation, altering the functions of a wide variety of modified proteins and affecting numerous physiological and pathological processes. This remarkable system and its numerous ramifications have been well reviewed elsewhere (21, 70, 647 654), and will not be addressed in detail here. Other forms of nucleocytoplasmic glycosylation have since been discovered and characterized functionally in many organisms. For example, oxygen sensing in diverse protozoa depends on prolyl 4 hydroxylation of the E3(SCF)ubiquitin ligase family subunit Skp1, and modification of the resulting hydroxyproline with a series of sugars. In the social amoeba *Dictyostelium*, O_2 availability is rate limiting for hydroxylation of newly synthesized Skp1. Knockout mutants of the Skp1 prolyl hydroxylase and each of the Skp1 glycosyltransferases confirmed that O_2 dependent post translational glycosylation of Skp1 promotes association with F box proteins and their engagement in functional E3(SCF)Ub ligases, which in turn regulate O_2 dependent developmental progression (655 659).

Returning to the extracellular compartment, another classic example is the modulation of IgG effector functions by the structural features of the *N* glycans in the IgG Fc region (660 663). Incomplete galactosylation of these glycans has been associated with chronic inflammatory diseases (664 666), and there are clear cut effects of IgG Fc glycan core fucosylation on antibody dependent cellular cytotoxicity (667 671) that are relevant to biotechnology (672 673). Sialylation of a minor fraction of the IgG Fc *N* glycans also appears to convert the IgG molecule into an inhibitor of inflammation, and is thought to underlie the anti inflammatory properties of therapeutically delivered intravenous immunoglobulin in humans. While many papers have been written about this effect, there is still some controversy about the extent of the effects, and the details of mechanisms in different models and species (674 701). One possible explanation for the confusing results is that the immune responses are subject to “hormesis”. This is poorly appreciated but common biological phenomenon wherein low and high doses of the same stimulus can result in opposite biological responses and outcomes (702 705). Regardless of controversies, it is clear that subtle changes in the glycosylation state of Ig Fc regions of *N* glycans can profoundly influence not only circulating half life, but also the effector function of antibodies (706). Meanwhile, contrary to 40 years of X ray crystallography suggesting immobility of the Fc region *N* glycan, recent NMR studies suggest that this glycan is actually mobile and dynamic in solution (707). Thus, it is possibly the range of motion of the glycan that is being altered by the various modifications, secondarily affecting interactions with Fc receptors of various types via an allosteric mechanism (708). Finally, while much of what is stated above refers to IgGs prepared for therapeutic use, it appears that modulation of IgG Fc glycosylation occurs naturally in vivo, in various inflammatory and infectious conditions (687)

although the mechanisms of modulation are largely unknown. More recent evidence suggests that the Fc region of other Ig classes may also alter effector function (709 710).

Epigenetic histone modifications

It is now clear that the addition of O GlcNAc residues to histone proteins surrounding chromosomal DNA is a key component of the histone code that regulates gene expression. O GlcNAcylation tar gets key transcriptional and epigenetic regulators including RNA polymerase II, histones, histone deacetylase complexes and members of the Polycomb and Trithorax groups. Given its dependence on cytosolic UDP GlcNAc levels, O GlcNAc cycling is thought to serve as a homeostatic mechanism linking nutrient availability to higher order chromatin organization. Evidence also suggests that this "sim ple" glycosylation mechanism can also influence X chromosome inactivation and genetic imprinting (650, 652 653, 711), which may be related to the fact that the O GlcNAc transferase is encoded on the X chromosome.

Extrinsic (interspecies) recognition of glycans

As mentioned earlier, it is not at all surprising that numerous patho gens and symbionts have evolved highly specific ways to recognize aspects of the dense and complex forest of cell surface glycans they encounter in host species. These interactions often involve glycan binding proteins (see Figure 3), and can result in symbiosis, com mensalism or disease, depending on the interaction in question and on the biological circumstances. A few examples from this vast field of knowledge are mentioned.

Bacterial, fungal and parasite adhesins

Among the numerous examples that can be cited for bacterial adhe sins (223, 712), the example of *Helicobacter* recognition of gastric sialoglycans is particularly interesting, given its role in pathogenesis of gastric ulcers and cancers (713 719). The F pilus mediated glycan dependent binding of uropathogenic *Escherichia coli* accounts for millions of urinary tract infections a year (720 721) and small molecule inhibitors are being explored as therapies or pro phylactics (722). With regard to parasites, a well known example is the merozoite stage of *Plasmodium falciparum,* which initiates mal aria via recognition of densely sialylated glycophorins on target ery throcytes (723 730), with the types of sialic acids presented affecting species specificity (731 733). At a later stage in malaria, heparan sulfate on endothelial cells mediates the binding of *P. falcip arum* infected erythrocytes via the DBL1α domain of PfEMP1 (734), likely accounting for some of the most serious complications of the disease. Specificity for host glycans also plays a role in the binding of a pathogenic fungus (*Candida glabrata*) to various target tissues (735).

It is notable that in many instances expert researchers eventually find "glycan independent" mechanisms of pathogen interaction with target cells and sometimes assume that the glycan dependent process is therefore unimportant. However, such studies are often done in static conditions with long contact times, making the initial glycan "handshake" less critical. The situation is quite different in real life, where opportunities for contact and infection may be transient and difficult. Of course, with increasing evolutionary time a highly suc cessful pathogen may come to rely more on glycan independent mechanisms, as appears to be the case with endemic *P. falciparum* infections (727, 736 738).

Viral agglutinins

By tradition, viral glycan binding proteins are called hemagglutinins, because many were originally discovered by virtue of their ability to agglutinate erythrocytes (which ironically are noninfectable, because they do not have the machinery for viral replication). Of these the best known is probably influenza hemagglutinin (the "H" in "H1N1"), which plays a key role in the infection process of this highly successful group of viruses. Much has been written about the specificity of the binding of these pathogens in relation to the sialic acid ligand, particularly the specific linkage to the underlying sugar chain, which determines the preference of the virus for avian versus human hosts (739 749). The evolution of the avian influenza viruses towards infecting humans involves selection for a change in binding specificity, which can be replicated experimentally (744). Interestingly, even our closest evolutionary cousins (chimpanzees) do not have a high density of human sialic acid composition or link age on their airway epithelium (750), explaining the lack of non human primate models and the unlikely choice of the ferret as a model for human influenza because it happens to express the human like linkage on its airway epithelium (751 752), and also because it turns out to, like humans, be missing the nonhuman sialic acid Neu5Gc (753). There are other examples of even more exquis ite sialic acid specificity of viruses, based on the presence of O acetyl esters at specific positions: while a 4 O acetyl ester on sialic acid tar gets is required for mouse hepatitis virus infection (754 756), a 9 O acetyl ester on the sialic acid side chain is required for the binding of certain other coronaviruses and influenza C and D viruses (624, 757 761). The difference between these two specificities is dictated by only a few key amino acid changes in the viral receptors (762 763).

Bacterial and plant toxins

Many soluble plant and bacterial toxins mediate their effects by binding to target glycans on cells of another species. Typically, a bacterial glycan binding B subunit is multimeric and serves to bring the toxic A subunit close to the membrane, whereby the latter then crosses over to mediate its toxic actions in the cytosol (with or with out prior endocytosis). Classic examples include cholera toxin, which binds GM1 ganglioside (256, 764), the infamous ricin toxin that binds to terminal β linked galactose residues (765 766), and the entero hemorrhagic *E. coli*/Shiga verotoxin that recognizes glo botriaosylceramide (Gb3Cer) and globotetraosylceramide (Gb4Cer) glycosphingolipids (767 769). The precise spacing of target ligands can be very important to the optimal binding of the pentameric lec tins to the target (770 771). The single oxygen atom difference between the Neu5Ac and Neu5Gc forms of sialic acids can also determine the specificity of toxin binding, such as in the cases of the typhoid (772) and SubAB (773) toxins. In some cases, there is also evidence of dual specificity, e.g., fucosylated blood group structures on glycoproteins may contribute to cholera toxin binding (774), via an independent binding site (775).

Soluble host proteins that recognize pathogens

Vertebrates also express toxic glycan recognizing peptides that can attack bacteria. For example, the small intestinal mucus layer is rich in RegIIIgamma, a secreted host antibacterial lectin, which is essen tial for maintaining partial sterility of a ~50 μm zone that physically separates the luminal microbes from the intestinal epithelial surface (776). Also, host galectins have been found to have unexpected

toxicity towards bacteria via recognition of their surface glycans (777 778). Killing occurs rapidly and independently of complement and is accompanied by disruption of membrane integrity. Galectin 3 may also play an important role in innate immunity against infection and colonization of *Helicobacter pylori*. (779). Galectin 1 can have dual and opposing effects on virus infection of human endothelial cells (780). In other instances, circulating soluble multimeric (typically pentameric) glycan binding proteins recognize surface glycans of foreign pathogens but do not directly kill the pathogen. Instead they provide a signpost to attract other active components of the immune system such as complement and macrophages. Examples including collectins like the mannan binding lectin, and the ficolins (334, 781). Indeed this kind of triggering of innate immune reactions via multivalent recognition of foreign glycans represents some of the most ancient and effective forms of immunity. For example, the hemolymph of horseshoe crabs recognizes invaders through a combinatorial approach, using lectins with different specificities against glycans exposed on pathogens (782), allowing these organisms to survive almost unchanged for >100 million years, without the benefit of adaptive immunity.

Pathogen glycosidases

Numerous pathogens generate a diverse array of cell surface and secreted glycosidases that serve to remodel or destroy the host glycocalyx, sometimes then utilizing the released monosaccharides as food sources and/or providing a nutritional resource for other microorganisms in the same milieu (783 785). Some mammals also rely on symbiotic microorganisms within their digestive tract to gain energy from plant biomass that is resistant to mammalian digestive enzymes (786). In other instances, the glycosidase acts in a balance with the binding activity of the same pathogen (787). For example, the sialic acid binding ("hemagglutinating", H) activity of the influenza viruses is balanced by the activity of its sialic acid releasing enzyme (neuraminidase, N), the latter working both to allow the virus to gain access to cell surfaces by cutting through interfering molecules (788 789), and also to allow release from cells after replication (790). The elegant structure based design of a modified version of the previously known sialidase inhibitor Neu5Ac2en (791) gave rise to the potent and specific inhibitor zanamivir (Relenza) (792 793), and later to the structurally related agent oseltamivir (Tamiflu) (794 795). It is worth noting that oseltamivir is not a glycan, showing how chemical shapes can be designed to mimic glycans. In yet other cases, microbial glycosidases remodel host glycans to generate the optimal receptor for subsequent binding. For example the secreted neuraminidase of *Vibrio cholerae* removes all but one specific sialic acid residue from host gangliosides, leaving behind the GM1 monosialoganglioside, which is the specific receptor for the B subunit of the AB5 exotoxin secreted by the same organism (796).

Host decoys

It has been suggested that circulating erythrocytes might act as non infectable decoy receptors for glycan recognizing viruses that gain access to the bloodstream (164). The thick layer of mucin glycans on the surface of epithelial cells lining hollow organs (139, 418, 448 452) also plays a critical role by providing decoy binding sites for pathogens, diverting them from their intended targets on the cells. Of course commensals may take advantage of such mucin binding to remain within their preferred ecological niche (797 800) and to favor dental biofilm development (801). But on the rare occasions when such bacteria accidentally find their way into the bloodstream, these same commensalism favoring adhesins become virulence factors, mediating interactions with platelets, which act as carriers of the organisms to eventual infection of damaged heart valves (798, 802 807). This is a recurring theme at sites of interspecies interactions, wherein factors favoring routine commensalism turn into potent "virulence factors", on the occasions when physical barriers are breached and/or host immunity is compromised.

Herd immunity

As discussed previously in the context of glycan evolution (164), herd immunity refers to a form of indirect protection from infectious disease, which occurs when a large percentage of a population is resistant to an infectious agent, effectively providing protection to individuals who are not immune. Since glycans are often the targets for many infectious agents, intra and interspecies polymorphisms in the expression of such targets can provide herd immunity, and restrict the spread of disease. As an example the ABO(H) blood group system can affect the spread of a highly infectious noroviruses that selectively binds one blood group structure and not another (808 811). This is likely why not everyone is sick by the time a cruise ship suffering a norovirus epidemic makes it back to port. ABO blood group polymorphisms also appear to affect susceptibility to cholera, as the cholera toxin has a secondary binding site for such glycans (775). The high levels of competitive oligosaccharides in human milk likely provide protection to breast fed infants against some viruses and toxins (812 814).

Pathogen-associated molecular patterns

It is now well recognized that innate immune cells also detect pathogen associated molecular patterns (PAMPs) using Pattern Recognition Receptors (815 816), particularly Toll like receptors (TLRs) (817 818), NOD like receptors (NLRs) (819 822) and C type lectins (823 826). Many PAMPs are glycoconjugates, e.g., bacterial lipo oligosaccharides or glycan based polymers, e.g., lipopolysaccharides and bacterial peptidoglycans, including bacterial DNA or viral RNA (which are (deoxy)ribose based polymers) (827 828). Glucan and oligochitin oligosaccharides released from fungal cell walls can also function as elicitors of plant defense (829).

Immune modulation of host by symbiont/parasite

In some instances, glycan molecules mediate symbiont or parasite modulation of host immune responses. For example, glycans such as polysaccharide A (an unusual pentasaccharide repeat), derived from important mammalian gut microbiome members, helps to modulate the host immune system into a more tolerant state (via T reg engagement) (213). Similarly, glycans derived from parasitic worms alter the immune status of their long term hosts (830), a process dubbed as "glycan gimmickry" (831).

Antigen recognition, uptake and processing

Antigenic proteins must first be taken up by antigen presenting cells (macrophages and especially dendritic cells), which process them into peptides, to be presented by MHC Class II molecules, for recognition by T lymphocytes. This process can be facilitated by glycans on the target protein. For example, the presence of high densities of terminal Man or GlcNAc residues on foreign proteins or microbes can trigger phagocytosis via C type lectins on antigen presenting cells, with resulting delivery of the antigenic proteins to processing

compartments (832 834). As another example, nonhuman α Gal (835) or Neu5Gc (836) residues carried on injected glycoproteins can result in immune reactions, and in the formation of immune complexes, which in turn can enhance immune reactivity against the peptide backbone. An alternative form of self/nonself recognition is exemplified by foreign glycolipid presentation by CD1 molecules, which are detected by restricted or invariant TCRs of NKT cells (837 842).

Bacteriophage recognition of glycan targets

The complexity and diversity of surface polysaccharides found on strains of a single bacterial species (>100 in the case of the pneumo coccus) (843) might be explained not only by selection for evasion of the vertebrate antibody response (844), but also by the need to evade attack by environmental bacteriophages (843, 845), which often use bacteria surface glycans as targets for recognition, and sometimes subsequent cleavage. While studies are continuing (846 849), this remains a poorly explored area. Given the very high dens ity of bacteriophages in nature (10 million viruses per milliliter of surface seawater!) (850), there are likely a huge number of such as yet undiscovered viruses with exquisite specificities for diverse gly can structures. Indeed, it is possible that a cognate bacteriophage exists for every variant of every bacterial surface polysaccharide that occurs in nature. Thus bacteriophages are effectively a massive reser voir of glycan binding and glycan hydrolyzing proteins still waiting to be exploited for glycan analysis and bacterial diagnostics as well as therapeutics (851), e.g., a potential new source of therapeutic "enzybiotics" (852) or disrupters of biofilms (853). Early steps in this kind of systematic search are promising (854).

Intrinsic (intraspecies) recognition of glycans

As mentioned earlier, numerous pathogens and symbionts have evolved highly specific glycan binding proteins that can recognize aspects of the cell surface glycans they encounter in host species. For a long time, examples of glycan binding proteins with clear cut func tions intrinsic to the same species (see Figure 3) proved elusive. Even when candidates such as the asialoglycoprotein receptor were found, their intrinsic functions were not obvious. Beginning with the dis covery of the specific functions of P type lectins in mediating lyso somal enzyme trafficking (discussed earlier), many examples of glycan binding proteins with intrinsic functions are now well known, and participate in a wide variety of functions. Only a few examples are mentioned below.

Intracellular glycoprotein folding and degradation

In addition to the biophysical effects of attached glycans on nascent glycoprotein folding discussed above, specific recognition of certain glycan residues plays a key role regulating the process of ER associated degradation (ERAD). After the unusual $Glc_3Man_9GlcNAc_2$ P P dolichol structure of the lipid linked oligo saccharide donor for N glycosylation was first fully defined (855), it turned out to be identical in almost all eukaryotes studied. Conservation of this structure for more than a billion years of evolu tion strongly suggested that it serves a very important purpose. But while many features of the structure were clearly needed to ensure optimal *N* glycan transfer (856 859), variations were possible in some parasites (860 861) and mutant cell lines (235), and the exquisite conservation of the native structure remained largely unex plained. A clue finally emerged when it was discovered that the third glucose residue on *N* glycans is repeatedly removed and then put back on again during glycoprotein folding in the ER (862 863). This in turn led to the discovery that this terminal glucose residue is recognized by certain ER chaperones, calnexin and calreticulin (864 868). The key role of this glucosylation/deglucosylation cycle in protein folding is now well established (63, 71, 869 878). However, even after the last glucose residue has been permanently removed, there are further steps of recognition of the oligomannose type *N* glycans that have been partially processed by ER mannosi dases (879 884). These recognition events are mediated in part by mannose 6 phosphate receptor homology domains in several chap erone proteins, as well as additional mannosidase like proteins and recognition complexes (130, 879, 881 888). Effectively, a byzantine array of glycan modifying and glycan recognizing proteins deter mines the final fate of a glycoprotein molecule in the ER whether it will be allowed to go forward into the Golgi pathway towards its final destination, or be consigned for ERAD. And since most pro teins that enter the ER are glycosylated, this system has a huge impact in normal and diseased states, as well as on unfolded protein stress responses (883, 889). As mentioned earlier, *O* mannosylation and *O* fucosylation can also play a role in monitoring the folding of newly synthesized proteins. Proteins that fail to fold are eventually removed from harmful futile protein folding cycles and prepared for disposal, via reverse translocation into the cytosol. There is even a sophisticated cytosolic pathway for removing and recycling the *N* glycans from misfolded proteins prior to the action of proteasomes, beginning with the action of a previously mysterious cytosolic Peptide: *N* glycanase (890). Notably *O* GlcNAcylation of nucleocy toplasmic proteins can also occur cotranslationally, protecting nas cent polypeptide chains from premature degradation by decreasing cotranslational ubiquitinylation (891).

Intracellular glycoprotein trafficking

As discussed earlier, the classic example of glycan roles in intracellu lar trafficking is that of the mannose 6 phosphate recognition system for the targeting of lysosomal enzymes to lysosomes. There is now evidence for other lectin like molecules within the ER Golgi path way, which likely modulate the trafficking of specific classes of gly coproteins. For example, the *LMAN1* gene product ERGIC 53 in the ER Golgi intermediate compartment is a mannose selective and calcium dependent human homolog of leguminous L type lectins (892) and acts as a critical chaperone for the coagulation factors V and VIII during their biosynthesis in hepatocytes (893) and endothe lial cells (894) respectively, also potentially affecting the biosynthesis of some other glycoproteins (895). Other examples are VIPL and VIP36 (896 901). Overall, it is reasonable to predict the existence of more such glycan recognizing proteins in the ER Golgi pathway, potentially involved in trafficking and/or chaperone functions.

Triggering of endocytosis and phagocytosis

A variety of cell surface receptors that recognize terminal glycans can trigger uptake of molecules (endocytosis), particles (phagocyt osis) or even intact cells. The classic examples are the asialoglyco protein receptor of hepatocytes and the mannose receptor of macrophages, mentioned in the introduction. A large variety of lec tins are known to carry out endocytosis in macrophages and den dritic cells. Such recognition processes may be critical not only for providing antigens to process and present to T cells, but also for clearing away damaged cells or glycoproteins, such as occurs when microbial sialidases enter the circulation during sepsis and cause

desialylation of platelets (902 903), or when cancers secrete incom pletely glycosylated mucins (512).

Intercellular signaling

In addition to the plant oligosaccharins already mentioned in the introduction, oligogalacturonides released from pectins can also act as regulators in plants (141, 904 906). Another well established example of intercellular signaling is represented by bacterial Nod factors (820) (not to be confused with the NLRs of vertebrate inflammasomes), which communicate signals between rhizobacteria and the roots of their leguminous plant hosts (907 911), initiating the symbiosis that is eventually responsible for the bulk of the nat ural nitrogen fixation on the planet a process key to the survival of many organisms that benefit from the resulting food chain. The chito oligosaccharides that transmit the signal show structural speci ficity for organism and host (907 908) and appear to be detected by a specific lectin (911). Transferring this capability into nonlegume crop species is obviously an exciting prospect. However, this may not be easy, since nonlegumes recognize the Nod factor via a mech anism that results in strong suppression of responses (912). In verte brate systems hyaluronan fragments released during injury can be detected by TLRs, thus triggering host immune responses (467, 913 915).

Intercellular adhesion

The mechanism of species specific recognition of disaggregated sponge cells has already been mentioned in the introductory sec tions. The selectin based system for cell cell interactions of leuko cytes, platelets and endothelial cells has also been discussed. The fact that oral fucose feeding results in correction of leukocyte adhe sion deficiency II by restoring selectin ligands provides the genetic proof of concept of this system in humans (385). The role of selectin interactions in a variety of normal and pathological conditions like inflammation and cancer is now understood (309, 916 921), and therapeutic approaches are in evaluation (921 923). One particu larly promising therapeutic outcome is based on the finding that selectins interact with sickled red cells and leukocytes in the circula tion to facilitate endothelial adhesion and other interactions (924 927) ultimately contributing to vascular occlusion and "sickle cell crisis" (928). The effectiveness of the pan selectin inhibitor GMI 1070 in reducing selectin mediated cell adhesion and abrogat ing crisis shows much promise in early clinical trials (922, 929). Another classic example is the role of Myelin associated glycopro tein (MAG, Siglec 4) in mediating key interactions between neurons and glia (930 932), a process critical for maintaining the stability of the myelin sheath that insulates axons (933 934).

Cell–matrix interactions

Evidence for critical matrix interactions with cell surface glycans can be found in the variety of muscular dystrophies resulting from altered glycosylation of the α dystroglycan ligand for major matrix proteins such as laminin, described in the introduction (191 204). In another example, hyaluronan matrices synthesized by stressed cells that recruit inflammatory cells are early events in many patho logical processes (935 936). Interestingly, this is a process that most if not all cells undergo, when dividing in a hyperglycemic environ ment. This phenomenon likely impacts experiments of many investi gators who use "standard" commercial tissue culture media, which actually have unphysiologically high amounts of glucose (937), at levels that might even cause diabetic coma in a patient.

Fertilization and reproduction

Many early studies suggested that glycan recognition processes were a critical part of many sperm egg interactions (75, 938 939). This field lagged behind for a while, partly because many researchers were looking for a single overarching glycan recognition mechan ism until the realization that species specific variations were in fact, exactly what one would expect! In a few instances such as in humans, specific glycans have now been identified as binding targets (940 941). Glycans also appear to be involved at many steps in the reproductive process, and in the processes of sperm migration to the site of fertilization (942). During the latter process, there is even evi dence that circulating antibodies can enter the uterine fluid and des troy sperm carrying nonspecies specific glycan antigens (943). After fertilization, there is evidence that glycans and glycan binding pro teins are involved in the processes of implantation (944) and placen tal functions (945 946) in mammals.

Clearance of damaged glycoconjugates and cells

Terminal sialic acids on circulating glycoproteins can be removed by endogenous sialidases during natural aging of the proteins (947), or suffer an attack by a pathogen expressing a sialidase. In either case, there would be exposure of underlying glycans recognized by spe cific receptors, such as the hepatocyte asialoglycoprotein receptor mentioned earlier. Data indicate that this kind of "eat me" signal may even mitigate the lethal coagulopathy of sepsis by clearing away damaged platelets (902 903). There also appears to be a very high capacity system for clearance of incompletely glycosylated mucins by the liver (512). Such molecules are released in large amounts by cancer cells, but could also potentially appear during damage to otherwise healthy organs. The subset of cancer derived molecules (e.g., CA125, Sialyl Tn and CA19 9) that survive such clearance then become useful markers of disease progression (948 951). The value of such markers for early detection remains unclear (952), a problem known to plague many predictive serum markers (953).

Glycans as clearance receptors

Glycans themselves can act as clearance receptors for other mole cules. For example, heparan sulfate proteoglycans in the liver space of Disse mediate clearance of triglyceride rich lipoproteins independ ently of the well known LDL receptor family members (954 955).

Danger-associated molecular patterns

Innate immune cells also recognize glycans released from tissue dam age in vertebrates such as hyaluronan fragments (467, 914 915) and some matrix proteoglycans (956 957) as danger associated molecular patterns (DAMPs) or "alarmins", triggering responses similar to those generated by exogenous PAMPs (see earlier discus sion). While fungal glycans can act as PAMPs to activate the host immune response, they can also instead mask other glycoconjugates to prevent such activation. Examples include *Candida albicans* (443, 958 959) and *Histoplasma capsulatum* (960).

Self-associated molecular patterns

As mentioned above, signals initiated by DAMPs and PAMPs are transduced via similar pathways, activating innate immune inflammatory responses. It was recently proposed that glycans could also act as self associated molecular patterns (SAMPs) (961), being recognized by intrinsic inhibitory receptors to maintain the baseline nonactivated state of innate immune cells, and to dampen their reactivity following an immune response. A clear example of glycan based SAMPs has been reported in the form of inhibitory Siglec recognition of cell surface sialoglycans (962 964), which may also provide a mechanism for the host to discriminate between infectious nonself and noninfectious self (965). Recent work (157, 966 968) has also affirmed prior evidence that sialoglycan recognition by factor H can blunt immune responses by inhibiting the alternate pathway of complement activation (966, 969). Siglec 9 recognition of hyaluronan may be another example of a SAMP system (970). Not surprisingly, these very same self glycans are also common candidates for molecular mimicry by commensals or pathogens that engage these inhibitory receptors (see below).

Antigenic epitopes

In addition to the blood groups already mentioned, intra and interspecies variations in glycosylation can result in strongly antigenic epitopes. Indeed a significant fraction of circulating Ig found in normal humans may be directed against foreign glycan antigens (971 973). Certain types of modifications of *N* glycans found on plant and invertebrate glycoproteins can trigger immune reactions in humans (974 977), including therapeutic glycoproteins (835 836). In a more complex scenario, individuals exposed to Lone Star tick bites seem to develop IgE antibodies against α Gal epitopes (humans do not have these epitopes). Upon subsequent exposure to mammalian foods that are rich in α Gal motifs (such as red meats), individuals react (sometimes severely) in an apparent "red meat allergy" (978 979). On another practical note, glycans like α Gal and the nonhuman sialic acid Neu5Gc represent the major xenoantigens that must be bypassed, to pursue the goal of xeno (pig organ) transplantation into humans. In pursuit of this difficult goal, α Gal and Neu5Gc double null pigs have recently been generated (980 983).

Xeno-autoantigens

It has recently been found that the nonhuman sialic acid Neu5Gc can become metabolically incorporated from dietary sources (particularly red meat) into certain cell types in the body, appearing on the surfaces of human cells as if it was synthesized by the individual (984 985). These "xeno autoantigens" are recognized by pre existing circulating "xeno autoantibodies", and the resulting "xeno sialitis" is suggested as one mechanism for the epidemiological association between red meat consumption and the exacerbation of some common disease states, such as carcinomas and complications of atherosclerosis (984 985). It would not be surprising if other examples exist. One can imagine for example that bacterial nonulosonic acids or plant monosaccharides that are structurally related to host monosaccharides might get activated to their corresponding nucleotide sugars and then get transferred onto endogenous glycans at a low rate. While the efficiency of such a process would likely be lower than that of Neu5Gc, the resulting immune responses might be even stronger.

Molecular mimicry of host glycans

Given that the host immune system recognizes typical glycans found on many pathogens are PAMPs and that endogenous glycans function as SAMPs, it is not surprising that microorganisms have evolved ways to achieve molecular mimicry of host glycans. What is remarkable is the striking extent to which such mimicry has been achieved, via all imaginable mechanisms. Just a few examples are cited here, with an emphasis on sialoglycan mimicry by vertebrate pathogens.

Convergent evolution of host-like glycans

It was originally thought that pathogen molecular mimicry was being achieved via vertebrate to bacterial gene transfer. While there is continued controversy about the extent of horizontal gene transfer between prokaryotes and eukaryotes (986), most instances of glycan molecular mimicry by pathogens seem to involve convergent evolution of pre existing pathogen biosynthetic pathways, or de novo generation of functional genes. Demonstrating the power of natural selection at the host pathogen interface, *Group B Streptococcus* polysaccharides (987) display identity to specifics of host glycan structure such as the Neu5Acα2 3Galβ1 4GlcNAcβ1 (which perfectly matches the structure of *N* glycan antennae on many human glycoproteins), and *Campylobacter* species carry out near perfect mimicking of complex brain ganglioside glycans (988 989). In the former case, it is evident that this mimicry allows the organism to imitate endogenous SAMPs and down regulate innate immune responses by engaging the inhibitory Siglecs (962). In the latter instance rare human immune responses against the ganglioside like structures can even result in serious illness, with the complement fixing antibodies damaging peripheral nerves (Guillain Barré syndrome) (990 991). While *Campylobacter* sialylation may also modulate immune responses via Siglecs during sporadic contacts with humans (992 995), it is unclear why the organism (which normally lives in the chicken intestine) (996) has evolved this remarkable degree of molecular mimicry of vertebrate ganglioside. Perhaps there are Siglec like inhibitory pathways in the chicken that have yet to be discovered.?

Appropriation of host glycans

Continuing with the example of sialic acids as host molecular mimics, microorganisms seem to have evolved every other conceivable mechanism to achieve this goal. These mechanisms range from the simple acquisition of host sialoglycans (997) to the direct transfer of host sialic acids by trans sialidases (998), to the highly efficient uptake of the small amounts of environmental free sialic acids (999) or even the direct utilization of trace amounts of CMP sialic acid present in host body fluids (968, 1000). In addition to acting as SAMPs recognized by Siglecs or limiting complement activation via factor H recruitment, such terminal sialic acids also serve to mask antibody recognition of underlying structures. The fact that numerous organisms have independently evolved so many different ways to decorate themselves with host like sialoglycans (1001) speaks to the strong selection pressure for this mimicry.

As with examples mentioned earlier, these "virulence factors" may actually represent attempts at commensalism and symbiosis, which become pathological in some circumstances. Many other examples of host glycan mimicry can be cited (1002), such as the bacterial re invention of hyaluronan (163, 1003), heparosan (the backbone of heparan sulfate) and chondroitin (the backbone of

chondroitin sulfate) (1004 1005). Interestingly, there appear to be limits to the "inventiveness" (constraints to convergent evolution) of microorganisms. Despite hundreds of millions of years of selection, no prokaryotes seem to have reinvented sulfation of glycosaminogly can backbones, nor recreated the difficult biosynthesis of the non human sialic acid Neu5Gc. While not exactly full blown "mimicry", most viruses simply take over and use the host glycosylation machinery to install glycans that mask and protect them from immune destruction. Examples of molecular mimicry by pathogens of plants or invertebrates need to be further investigated.

Multifunctional roles of the single type of glycan

The above classification of biological roles falls apart when one con siders certain glycan molecules that can mediate many different types of roles, depending on the circumstance. An example is the lipopho sphoglycan of *Leishmania* species, which is needed for establishment of initial infections in vertebrate hosts, and not for persistence or pathology (1006) but is later needed for binding to galectins located on the surface of midguts of their invertebrate vectors (1007). A more striking example is the myriad functions of heparan sulfate proteoglycans, with different roles being mediated by slight modifications of the molecule (155, 425, 427, 572, 628, 1008 1011). This is also exemplified by the widely disparate phenotypes arising from genetic modifications in various steps involved in bio synthesis of the molecule. Thus for example, mice deficient in hepar an sulfate 6 *O* sulfotransferase 1 exhibit defective heparan sulfate biosynthesis, abnormal placentation and late embryonic lethality (1012) and autism like socio communicative deficits and stereotypes appear in mice lacking heparan sulfate only in the brain (1013).

Even a structurally simple molecule like polysialic acid (an α2 8 linked homopolymer of *N* acetylneuraminic acid) can have a remarkable range of endogenous functions. For example, polySia has been implicated in numerous normal and pathological processes and phenotypes, including cell migration (1014 1016); cell differen tiation (1014, 1016); neurite outgrowth (1017 1019); blockade of myelination (1020 1022); binding and modulation of neurotrophin function (559, 1023 1025); alteration of synaptic plasticity (1026 1028); effects on learning and memory (1029 1032); facilitation of repair following injury (546 547, 1033 1036); schizophrenia pathogenesis (391, 1037 1042); major depression (553, 1043 1045); bipolar disorder (391 392, 1044); alcoholism (1046); epi lepsy (1047 1048) and social interaction (1049).

Some questions and issues arising

Some readers will likely feel that the examples of biological func tions discussed are not the most striking ones, and others will doubt less complain that numerous additional functions have not been mentioned. Such deficiencies and limitations are simply an indica tion of how far the field has come in the last 20+ years since the last review in 1993. Let us conclude this incomplete attempt by discuss ing some questions and issues arising, and some future prospects.

Why did glycans become the preferred cell surface covering during evolution?

With the possible exception of transient bloodstream phase of cer tain parasites, there appears to be no exception thus far to the "rule" that the surfaces of all cells in nature are covered with a dense and complex coating of glycans, which is taxon , species and cell type specific (178). If it had been biologically possible to evolve a living cell devoid of such a coating, such a cell would have no doubt emerged from >3 billion years of evolutionary selection. There is no single best explanation for this ubiquity of cell surface glycans, and several mutually nonexclusive ones can be considered. In addition to providing a physical barrier to protect the plasma membrane, glycans tend to be hydrophilic, often do not have rigid structures, and instead have significant freedom of motion in aque ous solution. These are the optimal properties for a class of mole cules that interact at the interface with an aqueous environment. Also, it is difficult for cells coated only with proteins to evolve and escape mechanism from a pathogen that binds to a specific cell sur face protein. Most amino acid changes are not usually well tolerated by proteins, impacting folding and/or stability or even rendering the molecule dysfunctional. In contrast, most intrinsic glycan functions are mediated not by a single absolutely required sequence, but by an ensemble of structures, spanning a continuum. Even the apparently "lock and key" example of Man 6 P recognition of lysosomal enzyme *N* glycans discussed earlier actually involves a spectrum of Man 6 P bearing structures with a range of binding properties to two different M6PRs. In other words, many glycan functions are "analog" not "digital". Thus, it is easier for a host to escape patho gens by subtly changing glycosylation (i.e., glycans may convey more robustness to the organism) without drastically altering intrin sic functions. Last but not least, a vastly greater number of struc tural variations can be generated via monosaccharide oligomerization and branching in comparison with nucleic acids or amino acids (1050). This increases the odds of evolutionary selec tion to escape from a cell surface interacting pathogen or toxin.

Red Queen effects in glycan evolution?

Given the above considerations, it is reasonable to suggest that gly cans are particularly prone to Red Queen effects (running to stay in one place) (164). As illustrated in Figure 4, one can envisage several such effects involving glycan interactions, leading to a delicate bal ance between preserving endogenous function and evading pathogen attack (170). A more nuanced and sophisticated view that takes into account additional evolutionary considerations can be found in Figure 5 (173).

What is the significance of lineage-specific deletions or additions of specific glycans?

In contrast to the genetic code, there are many more species specific variations in glycans, ranging from entire classes of glycoconjugates, e.g., sulfated glycosaminoglycans not found in prokaryotes, to spe cific glycans, e.g., the absence of α Gal epitopes in old world mon keys (1051), and the independent losses of the sialic acid Neu5Gc in humans (1052), new world monkeys (1053), mustelids and related taxa (753), and apparently in sauropsids (the ancestors of birds and reptiles) (1054). In every instance of apparent lineage specific loss, a careful phylogenetic analysis is needed to ascertain if the differences are due to gain or loss of a specific gene or pathway and/or due to convergent evolution (or particularly in the case of prokaryotes, horizontal gene transfer). Regardless of the underlying mechanisms, more studies are needed to understand not only the functions of taxon specific glycans but also the biological significance of their loss in some lineages. Some data suggest that taxon specific glycan losses may have played a role in protection from parasites like mal aria (732, 1055), and even in speciation events, such as the origin of the genus *Homo* (943).

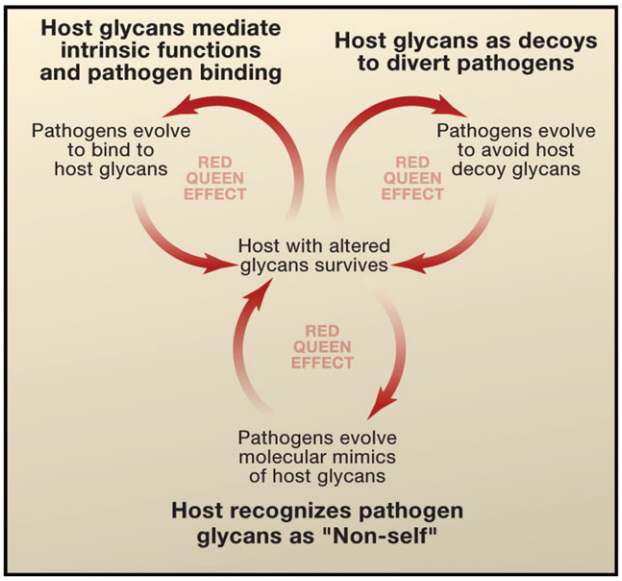

Fig. 4. Red Queen effects in the evolutionary diversification of glycans. Each arrowed circle represents a potential evolutionary vicious cycle, driven by a Red Queen effect, in which hosts are constantly trying to evade the more rapidly evolving pathogens that infect them. Hosts require glycans for critical cellular functions but must constantly change them to evade glycan-binding pathogens, and yet do so without impairing their own fitness. Hosts also produce soluble glycans such as mucins, which act as decoys to divert pathogens from cell surfaces; but pathogens are constantly adjusting to these defenses. Hosts recognize pathogen-specific glycans as markers of "non-self," but pathogens can modify their glycans to more closely mimic host glycans. There are also possible secondary Red Queen effects involving host glycan-binding proteins that recognize "self". In each of these cycles, hosts with altered glycans that can still carry out adequate cellular functions are most likely to survive. Reproduced with permission from Varki A. 2006. *Cell*. 126:841 845. Copyright Elsevier.

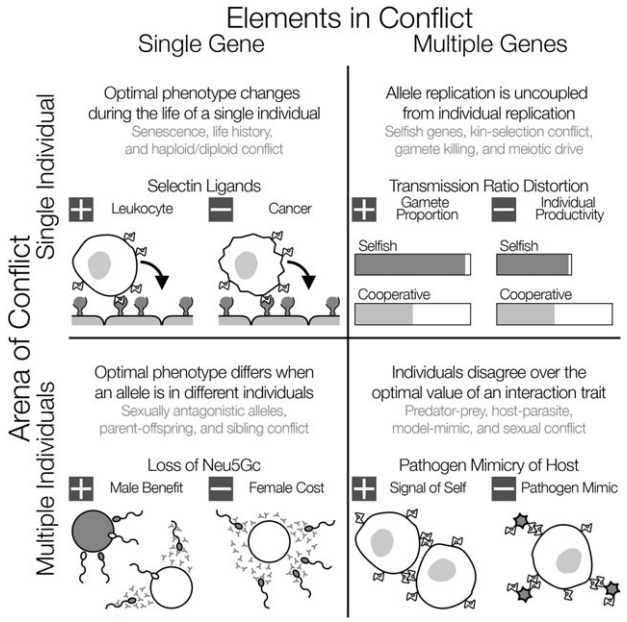

Fig. 5. Evolutionary conflicts between alleles and individuals. For single allele-single individual, single alleles conflict with themselves when their positive effects in one context cause negative effects in another. Some examples are here. Selectins on epithelial cells bind glycans on leukocytes and guide them to sites of inflammation, but this can also be exploited by cancer cells. Regulatory or functional changes that separate conflicting tasks are expected to evolve in response. For single allele-multiple individuals, conflicts can extend across individuals that share an allele. Females that lack Neu5Gc raise antibodies against it. Males that lack Neu5Gc have higher rates of fertilization, and females have lower rates. Individual-specific regulation could resolve these conflicts. For multiple genes-single individual, selfish alleles can bias reproduction in their favor at the cost of individual reproduction, causing conflict with other genes in the genome. Mutant alleles that favor heterozygotes are passed more often than expected but increase the risk of congenital disorders of glycosylation. Other genes are selected to suppress the selfish allele, often by modification of chromosomal recombination and linkage. For multiple genes-multiple individuals, molecular markers of self cause cells to direct benefits toward identical genetic relatives, but they can be exploited by pathogen mimics. Co-evolution is a common outcome, as hosts develop more reliable markers of self, and pathogens develop more effective molecular mimics. Reproduced with permission from Springer and Gagneux, 2013, *J Biol Chem*, 288:904 6911.

Why did evolution select *O*-GlcNAc as the dominant form of intracellular eukaryotic glycosylation?

In striking contrast to the bewildering diversity of extracellular gly cosylation, there seems to be a limited number of forms of intracel lular glycosylation, with a single modification (*O* GlcNAc) numerically dominating the scene (647 648). One possible explan ation is that this intracellular environment is not subject to selection pressures by myriad pathogens that express diverse and specific glycan binding proteins. More specifically with regard to *O* GlcNAc it has been suggested that the donor molecule UDP GlcNAc acts as an optimal metabolic sensor for multiple pathways, i.e., uridine, phosphate, glucose, nitrogen and acetate (649, 651 653).

Do free oligosaccharides in the cytosol and serum have specific functions?

During the N glycosylation of glycoproteins in the ER, considerable amounts of unconjugated polymannose type glycans are generated from breakdown of the lipid linked precursor (1056). Later, mis folded glycoproteins that are returned to the cytosol for proteasomal degradation are first subject to a cytosolic PNGase enzyme that releases free oligosaccharides (890). Such free oligosaccharides are then subject to either further cytosolic catabolism or pumped back into lysosomes for degradation (1056). Even free complex *N* glycans bearing sialic acids can also be found in the cytosol (1057). The question arises as to whether such glycans mediate any specific func tions in the nucleocytosolic compartment, before they are degraded, such affecting transcription. Meanwhile, free sialyloligosaccharides related to *N* glycans have recently been found in serum (1058), and may also have novel functions yet to be discovered.

Can a glycan-binding protein recognize more than one class of glycan?

Glycan binding proteins are often discovered based on their recogni tion properties, and given names related to their initially discovered binding targets, e.g., Galectins bind β galactosides (323), and Siglecs recognize sialic acids (329). However, many examples have emerged wherein well known glycan binding proteins are discovered to also bind to unrelated glycan class, sometimes not even obviously similar in structure. In some instances, this is simply because the protein in

question has two distinct binding modules, e.g., the L type lectin mannose receptor can also have a separate R type lectin module that recognizes sulfated GalNAc residues on pituitary glycoprotein hormones (1059). However, in many other cases, the binding region is shared or very close by. Thus for example, selectins that were originally defined by their binding to sialylated fucosylated glycans can bind quite well to certain subsets of heparan sulfate glycosaminoglycans (1060 1061). Likewise, Fibroblast Growth Factor 2 can bind both to polysialic acid and heparan sulfate (1025), and Siglec 9 binds both sialic acids and hyaluronan (970). Recently, it has even been shown that some galectins bind efficiently to as yet undefined motifs on bacterial surfaces (777) as well as to some sulfated glycosaminoglycans (1062), in a manner still inhibitable by its canonical ligand lactose. In most such instances, it is unclear what the shared glycan motif is. Given great dissimilarities in primary structure, cross recognition perhaps arises from "clustered patch" combinations (146, 302) of components of more than one monosaccharide, such as hydroxyl, carboxyl, sulfate, acetyl groups, etc. Given existing difficulties in efficiently incorporating even small, defined cognate ligands into the binding pockets of crystal structures of glycan binding proteins, it will be challenging to compare such disparate ligands and define the shared recognition components. Regardless, it is clear biological functions of a glycan binding protein should not be assumed to be mediated by the canonical glycan ligand class that originally defined the name of the protein.

How many more glycan-binding proteins are there yet to be discovered?

Regarding extrinsic (interspecies) binding proteins, it is reasonable to predict that for every specific glycan found on the cell surfaces of a host there is somewhere, a pathogen or symbiont that has developed an exquisitely specific binding protein for the glycan. Indeed, if this vast array of binding proteins could be isolated and converted into useful probes, one could have a new approach to "glycomics", which actually studies the intact (naturalistic) glycome, in a manner that is exactly as it is "seen" by binding proteins in nature. The first steps in this direction have already been taken, and the results are very promising (1063 1066).

With regard to intrinsic (intraspecies) binding proteins, the situation is less clear. However, the serendipitous mechanism by which many of them have been discovered suggests that a systematic approach to future discovery may be useful. Consider the case of sialic acid binding proteins. As late as the 1970s, it was thought that sialic acids were just biological masks, and that there were no binding proteins intrinsic to the organism synthesizing them. Notably of the few sialic acid binding proteins reported since then, i.e., Factor H (1067 1068), Selectins (286), Siglecs (324 325), PILRs (1069) and PECAM 1 (1070 1071), almost all were discovered serendipitously to recognize sialic acid, based on an unexpected loss of a functional readout upon sialidase treatment. Given that sialic acids have been present on the glycocalyx of the Deuterostome lineage of animals for more than 500 million years, it would not be surprising if there are many more as yet undiscovered sialic acid binding properties of other already known proteins. The same is likely to be true for other classes of glycans, especially terminal and exposed structures. On the other hand, given relatively low single site binding affinities, a systematic approach to discovering such proteins may not be trivial. Sialoglycan array studies recently revealed the sialic acid binding properties of M ficolin (1072). On a cautionary note, the very high density of targets in glycan arrays might also detect binding specificities that may not exist in nature.

Is glycan recognition by proteins really of "low affinity"?

Compared to protein protein interactions that typically have measured binding affinities in the nanomolar range, studies of important glycan protein interactions usually give values in the micromolar, or even millimolar range. While there can be a high degree of recognition specificity, the single site affinity is typically poor. Various reasons are discussed, and this general observation underscores the frequent need for multivalent avidity, in order to generate effective biological functions or effective experimental probes (1073). Of course, multivalency is the general state of most biology at the cell surface as nothing is present in only one copy. Thus effective affinity in nature is actually quite high. Regardless, in reality most glycans in aqueous solution are in constant motion and constitute an ensemble of many different shapes generated by many mobile bond angles, which are constantly interchanging (1074 1075). In order for the more rigid and ordered binding pockets of glycan binding proteins to bind such "shape shifting" glycans, they must actually "trap" one of the numerous possible solution conformations of the cognate glycan into the pocket, where the immobilized glycan can be seen in a crystal structure. Strictly speaking then the effective concentration of the true cognate glycan is far lower than that of the total glycan concentration, likely in the nanomolar range. Exceptions may arise when the glycan targets are restricted in their motion, forming "clustered saccharide patches", such as on the surface of densely glycosylated cells, mucins or viruses (146, 544).

Can we better define and name specific glycoform ligands for glycan-binding proteins?

In some cases, the natural ligands for glycan binding proteins can be defined by the primary sequence of the cognate glycan, e.g., the *Sambucus nigra* agglutinin binds the motif Siaα2 6Gal(NAc). However, in other instances the ligand is a specific glycoform of a particular glycoprotein, which is difficult to define in terms of a cognate glycan sequence. This results in the inadvertently erroneous statements, implying that the polypeptide is the ligand, e.g., "PSGL 1 is the ligand for P selectin" (1076); or "CD24 is the ligand for Siglec 10" (965) (PSGL 1 and CD24 are actually the designated names of the core polypeptides). It also leads to incorrect assumptions, e.g., that a glycoform of CD24 must automatically be the ligand for mouse Siglec G, the mouse ortholog of human Siglec 10 (965). In these and many other such instances, the ligand is actually a specific glycoform of the named polypeptide, and is only synthesized by certain cell types with the right kind of glycosylation machinery, i.e., the same carrier polypeptide does not serve as a ligand in other situations. In the case of a CD44 glycoform from hematopoietic stem cells that is a specific ligand for E and L selectin (1077 1078), the authors reasonably chose to rename the molecule altogether as HCELL (hematopoietic cell E and L selectin ligand) (921). However, this leaves out the useful information that the underlying polypeptide is CD44. A compromise may be to list the name of the polypeptide and use the superscript to indicate that it is a specific glycoform that generated the ligand in question, e.g., $CD44^{HCELL}$ or $HCELL^{CD44}$. As with most nomenclature issues, it may be hard to find consensus on this matter. Suffice it to say that

there is need for a resolution, to make it easier to understand the lit erature on ligands for glycan binding proteins.

Why has it taken so long to elucidate biological roles of glycans?

It is clear that glycans got "left out" of the initial phase of the molecular biology revolution of the 1980s, not only because they were more complex and difficult to study, but also because they were not part of the original "central dogma" (1079). This resulted in a peculiar distortion of the bioscience community, in which an entire generation of biologists (beginning in the 1980s) has been trained without much knowledge or appreciation about the struc ture, biosynthesis and roles of glycans in nature (1080). The relative lack of interest in glycans can also be partly traced to the early lack of understanding of their biological roles. So, why was it so difficult to elucidate biological roles of glycans? Some of the reasons are obvious, such as the technical difficulties in detection, analysis and manipulation in biological systems. Some additional considerations are outlined in Figure 6. Because of the information embedded in the template driven biosynthesis of nucleic acids and proteins, it has been relatively easy to go from one to the other, using sophisticated yet facile experimental methods, and via bioinformatic predictions. Also as shown in the upper panel of Figure 6, the path to defining a specific function as being mediated by a specific protein has been relatively straightforward. In striking contrast the field of glycos ciences originated in "descriptive" carbohydrate chemistry and bio chemistry and remained in these domains for a long time. New glycans were discovered by a variety of means (such as those shown in lower panel of Figure 6) and their structure and biosynthesis were elucidated. Studies of changes in development and disease were almost guaranteed to show interesting findings, justifying further funding and research. It was also necessary to decipher the biosyn thetic enzymes and mechanisms involved in generating each glycan. Thus there was plenty of interesting work to do, other than take on the most difficult task of elucidating function. Also, many of the functions of glycans tend to be "analog" and not "digital", and many glycans have more than one disparate function. Finally, the rapid evolution of glycans has generated a lot of species specific dif ferences, making it difficult to find common themes applicable to all major model systems studies in biology. With the power of modern glycomics and the move to integrate glycosylation data into multio mic studies, it now possible to get past these difficulties and study the functions of glycans like never before. But we still then need to define the glycome.

What is the glycome?

It is clear that the glycome of an organism is far, far more complex than that of its genome, transcriptome or proteome, and it is only recently that "glycomics" has become practically feasible (1065, 1081 1089). Daunting and sophisticated as it is, most of what is called glycomics in 2016 still amounts to generating a "parts list" of all the glycans one can find in a given cell type or tissue at a particu lar point in time and space, i.e., similar to a peptide map of a mix ture of proteins. In addition, current methods partially or completely destroy or miss labile modifications like acetylation, sul fation, phosphorylation, lactylation, pyruvylation, etc. More efforts are needed to discover all the glycan attachment sites on proteins and lipids, in a cell type in question (1089). Eventually, we need not only to define all of the above, but also to understand and visualize the conformation and organization of glycans on

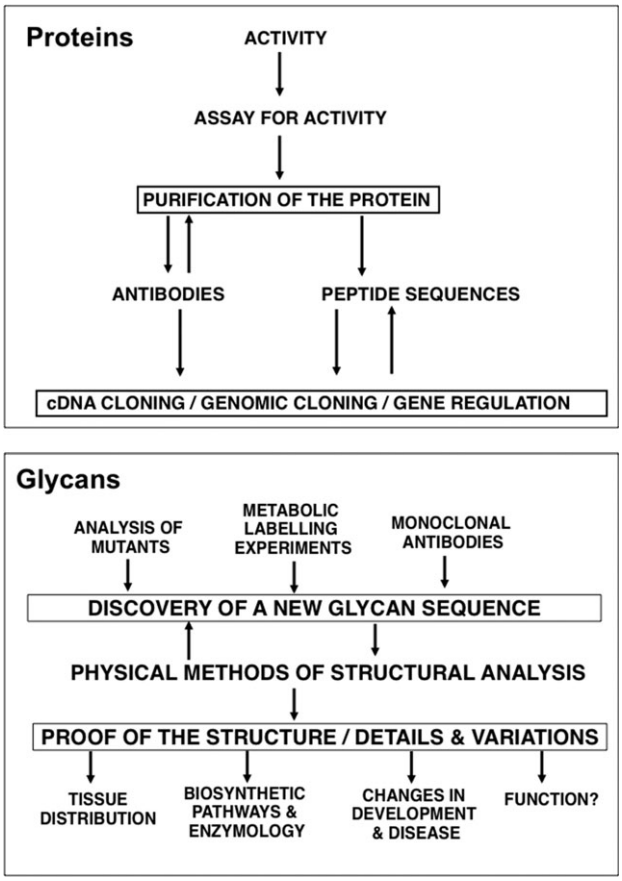

Fig. 6. Contrasts in early approaches to the discovery and characterization of proteins and glycans. Compared to the robust and relatively easy interdirectional progress in the early study of proteins, often originating from initial knowledge of their functions (upper panel), early approaches to the discovery and characterization of glycans (lower panel) did not often originate from functional clues. See text for discussion.

individual cell types and surfaces, in the form of "clustered sacchar ide patches" (146, 302), or glycosynapses (87). In the final analysis, full understanding of the biology of glycans will require this compre hensive type of view for which analytical techniques are yet to be defined. But great advances are being made by many investigators in all of the above levels of glycomics, and the future looks bright. Moreover, we can take advantage of the fact that pathogens and commensals have already spent million of years adapting to interact with the glycans of their hosts, and have already evolved highly spe cific binding proteins for recognition. Thus as mentioned earlier, an entire array of probes for defining the glycome is already available in nature, waiting to be isolated, characterized and eventually con verted into practical tools, if necessary with further mutations. Initial steps in this direction are also very promising (1090).

What biological roles do glycans not mediate?

This rhetorical question seeks to emphasize that the biological roles of glycans are highly varied, and span the spectrum of possibilities. So the exceptions are few. So far there does not seem to be an example of multigenerational information transfer directly mediated by glycans, such as that mediated by DNA or RNA. But it has recently become evident that *O* GlcNAc can modify RNA polymer ase II, histones, histone deacetylase complexes and members of the Polycomb and Trithorax groups (1091 1092). Thus, it is suggested

that O GlcNAc cycling serves as a mechanism linking nutrient avail ability to chromatin organization, histone modification and epigen etics (711). It remains to be seen if such epigenetic effects can mediate intergenerational transfer, in a manner similar to other epi genetic marks. There are also no clear cut examples of glycans act ing as enzymes [if one excludes RNA from being considered as a polysaccharide, and intramolecular self cleavage of PolySia (1093) as a chemical anomaly].

Why the persisting lack of attention to this fundamental component of biology?

Glycans are a major and integral part of all biological systems, and >3 billion years of biological evolution has failed to generate any life form on the planet that is not absolutely dependent on glycan chains for its existence. Yet the current situation is comparable to that in cosmology, with a standard model based on extant knowl edge that functioned well until it was realized that the bulk of the universe consists of dark energy and dark matter, which had been previously ignored. In effect, glycans have become the "dark mat ter" of the biological universe (1094), important yet poorly under stood and therefore deserving special attention. However the levels of funding, the number of scientists involved and the scientific popu larity of Glycosciences remain low. Many of the reasons are evident from the foregoing discussion. As mentioned earlier, a major issue is the fact that an entire generation of scientists has been trained with a limited knowledge of this class of molecules, and they are unlikely

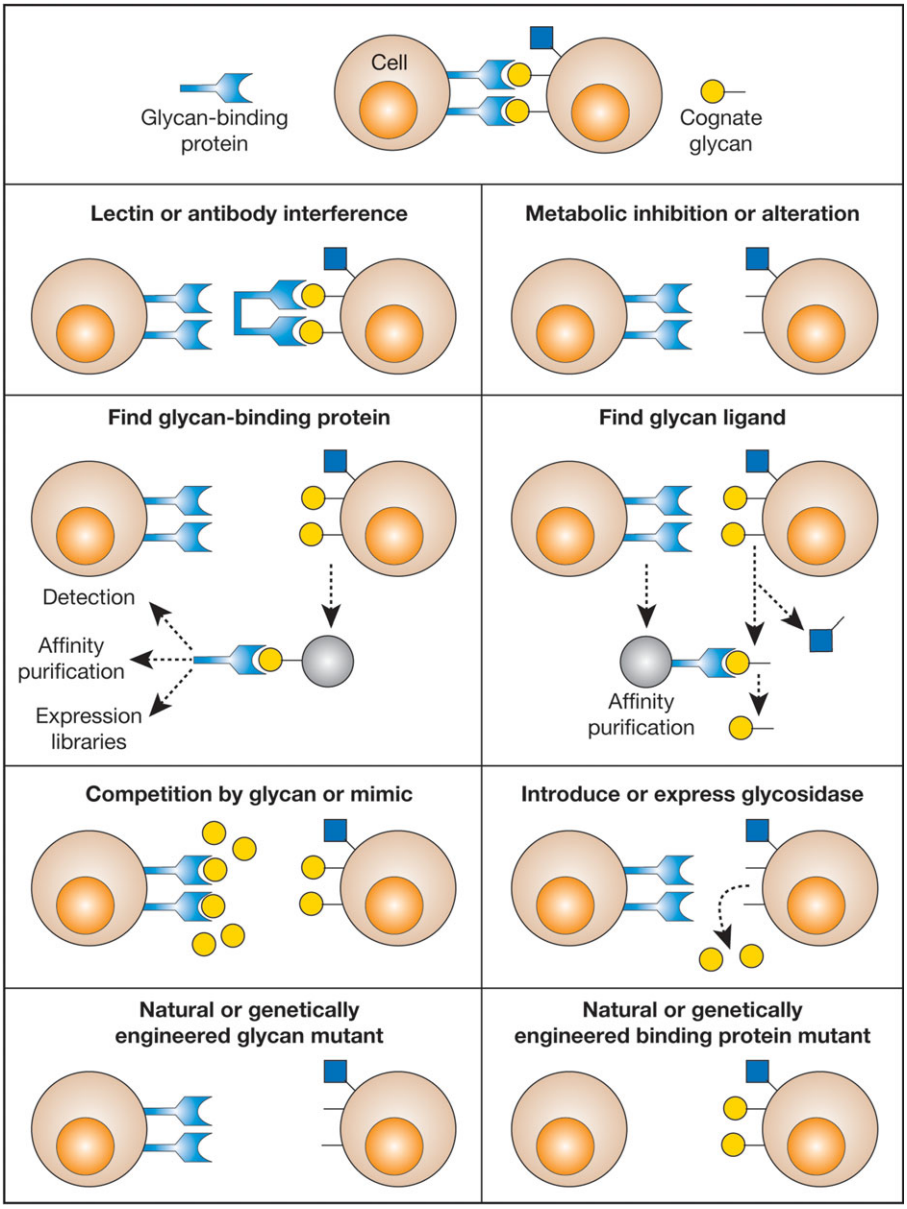

Fig. 7. Approaches towards elucidating biological roles of glycans. The figure assumes that a specific biological role is being mediated by recognition of a certain glycan structure by a specific glycan-binding protein. Clues about biological roles could be obtained by a variety of different approaches. For detailed discussion of each approach, see the original reference. Not shown are newer methods taking advantage of the power of chemoenzymatic synthesis and the introduction of modified sugars with bioorthogonal reporter groups into biological systems. Drawing by R. Cummings, updated from ref. 160 with permission from the Consortium of Glycobiology Editors.

to now turn to studying them. Thus, a new generation of young minds needs to be educated, in this aspect of biology. The other major factor is the lack of easily available technologies for the synthesis and analysis of glycans. In this regard, the 2012 US National Academies/National Research Council report on the future of glycoscience concluded by recommending: "…transforming Glycoscience from a field dominated by specialists to a widely studied and integrated discipline, which could lead to a more complete understanding of glycans and help solve key challenges in diverse fields", and emphasized the need to invest in education and technology development (1095). A more recent NIH working group report further emphasizes the need for training in Glycoscience (1080).

Future prospects

Many functions of glycans will continue to be discovered by the conventional processes of scientific investigation that will serendipitously come upon such functions. However, there are several potential systematic approaches to uncovering these functions that are depicted in Figure 7. Each approach has its pros and cons, which are discussed in detail elsewhere (160). Also not fully shown in this figure are newer methods taking advantage of the power of chemoenzymatic synthesis (62, 127, 158) and introduction of modified sugars with bioorthogonal reporter groups into biological systems (111). As with any biological questions, there are pros and cons of studying isolated cells versus intact organisms. And one must always ask how species or taxon specific a given function might be. All of approaches depicted in Figure 7 are rendered difficult in the case of glycan types that have numerous nonoverlapping functions in the same biological system. As the late Philip Majerus once put it, trying to decipher the roles of such molecules by preventing their synthesis or by destroying them after the fact is like "sifting through the ashes to find out how dynamite works". Of course this problem is not unique to glycans. Complexity and pleiotropy are inherent in all of biology, and the same could be said of other post translational modifications.

One would have to go back very many decades to find reviews about "biological roles of nucleic acids" or "biological roles of proteins". The fact that such a review on roles of glycans was necessary in 1993 indicates how far behind we were in our understanding of their biology. As this update after 23 years shows, we have come a very long way, and one author now can barely scratch the surface of the topic in a single review. The time has come for the biology of glycans to be "mainstreamed" with that of the other major macromolecules that are universal to all life forms. But this requires a concerted effort on the part of all biologists and naturalists, to fully integrate the roles of glycans into their thinking about living systems. Once that happens, there will no longer be any need for writing another review like this one.

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Conflict of interest statement

None declared.

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