The Glycobiology of Infectious Disease

Fundamentals in Glycobiology

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Today

Review the roles of glycans in the immune system

Discuss examples of the roles of glycoconjugates in host-pathogen interactions

Highlight the roles glycans can play in evading the immune system

Glycans and Vaccines

Nature Reviews Microbiology 4, 229-236 (March 2006)

Glycans in the Immune System:

• Play roles is differentiating self- and from non-self

• Mediate many pathways associated with the immune system, such as the homing of leukocytes (etc) to sites on inflammation

• Act as physical barriers and as decoys

Kidney in cancer pathogenesis and cancer therapy Glent Drainhoff Nature Reviews Cancer 6, 11-22 (January 2006)
Many antigens that define self, such as the ABO blood group antigens depend on carbohydrates

- The ABO system was discovered in the twentieth century by Karl Landsteiner and colleagues.
- They took sera from different patients and looked at the ability to agglutinate blood.
- “Curiously enough the reactions with normal human isoagglutinins do not occur in a, so to speak, haphazard manner but they separate the human bloods into four sharply defined groups designated as O, A, B, and AB.” — Landsteiner and Levine, 1928.

Karl Landsteiner
Nobel Prize in Physiology or Medicine in 1930.

ABO antigens are covalently bound to membrane glycoproteins and glycolipids (type-1 or type-2 N-acetyllactosamines, on O-GalNAc glycans or on glycolipids)

These are not only found on the surface of red cells, but in other tissues including the vascular endothelium and a variety of epithelia.

ABO antigens can also be attached to secreted on secreted glycoproteins, glycolipids, and free glycans.

On each red blood cell approximately 1–2 million ABH determinants (~80% of the total) are attached to the anion transport protein (also known as band 3).

Glycans Found in Other Mammals, but NOT Humans

- All other mammals, including chimpanzees, make and utilize N-Glycolyneuraminic Acid.
- Unlike other mammals humans don’t add galactose α1-3 to galactose.
- In humans neutralizing antibodies exist for both carbohydrate structures.
Humans can't make CMP-N-Glycolyneuraminic Acid

Humans are genetically deficient in Neu5Gc due to an Alu-mediated inactivating mutation of the gene encoding the enzyme CMP-N-acetylneuraminic acid (CMP-Neu5Ac) hydroxylase (CMAH).

The Galα1-3Gal epitope

- Galα1-3Gal is synthesized on type-2 units on glycolipids and glycoproteins
- This epitope is found on the glycoconjugates of new world primates and other mammals, but NOT old world primates and Homo Sapiens
- Humans (and old world primates) carry antibodies in their serum to this protein
- The presence of this carbohydrate structure is a major obstacle for using non-primates for xenotransplantation
- Unfortunately, while tissues from the α1,3galactosyltransferase 3 knockout don't experience hyperacute rejection, they do experience humoral xenograft rejection (3-months).

What are the remaining challenges?

- NeuGC?
  - Parcine cardiac valves are regularly used – but these are cleansed of human cells. It is unclear of there is remaining NeuGC in the connective tissue matrix.
  - Using a “human-like” mouse model which is NeuSGC deficient; research induced a NeuSGC antibody response before allotransplantation of NeuSGC alets. Mice with antibodies rejected the tissues.

Humans will utilize N-Glycolyneuraminic Acid in their food and this has been linked to inflammation

It's not all bad, some microbes use N-glycolyneuraminic acid to promote their colonization

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Glycans in the Immune System:

- Play roles in differentiating self- and from non-self
  - Innate Immunity

- Mediate many pathways associated with the immune system, such as the homing of leukocytes (etc.) to sites on inflammation

- Act as physical barriers and as decoys

Many Functions in Both the Innate and Adaptive Immune Responses Rely on Protein Carbohydrate Interactions

Galectins, which are multivalent glycan binding proteins, have numerous roles in including in pathogen recognition, regulating inflammation and the modulation of the adaptive immune response
and the activation of downstream signaling. CD14 is a GPI-anchored membrane protein and LPS binding protein (LBP) mediates the recognition of LPS by the innate immune system. LPS is a major component of the outer membrane of Gram-negative bacteria. LPS consists of a lipid A core, and a distal polysaccharide (O-antigen) (Figure 3). The lipid A core is composed of a hydrophobic backbone with alternating phosphate esters and ketone groups, which are essential for the lipopolysaccharide (LPS) to CD14. CD14 is a GPI-anchored membrane protein and LPS by the innate immune system occurs via LPS-binding protein (LBP) that recognizes LPS and transfers it to CD14.

In the following sections, we describe the most important bacterial conserved structures that are recognized by the innate immune system. These conserved structures are known as pathogen-associated molecular patterns (PAMPs).

- **Pathogen-associated molecular patterns**
  - One mechanism of innate immunity recognizes molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells.
  - These unique microbial molecules are called *pathogen-associated molecular patterns* or PAMPs.

**Innate immunity**

- **Innate immunity**: antigen-nonspecific defense mechanisms that use immediately or within hours after exposure to an antigen.
- Other than physical barriers, innate immunity can be thought of as:
  - The professional phagocytes,
  - The complement system,
  - and the antimicrobial peptides.

**Overview of carbohydrate recognition molecules of the innate immune system.**

PAMPs include LPS (gram-negative) peptidoglycan and lipoteichoic acids (gram-positive), mannose (common at the termini of microbial glycolipids and glycoproteins), bacterial and viral unmethylated CpG DNA, bacterial flagellin, the amino acid L-formylmethionine found in bacterial proteins, double-stranded and single-stranded RNA from viruses, and glucans from fungal cell walls.
Glycans in the Complement Pathway

The complement system plays a crucial role in the innate defense against common pathogens. Activation of complement leads to robust and efficient proteolytic cascades, which terminate in opsonization and lysis of the pathogen as well as in the generation of the classical inflammatory response through the production of potent proinflammatory molecules.

Activation of immune signaling by bacterial lipopolysaccharide (LPS)

LPS is bound by the pattern-recognition molecule Toll-like receptor 4 (TLR4) in conjunction with the cell-surface receptor CD14. Recognition of LPS activates the secretion of pro-inflammatory cytokines.

In addition, intracellular glycosylation appears to regulate the NFκB signaling pathway at multiple points.

MBL is a 6- to 18-headed molecule that forms a complex with MASP-1 (Mannose-binding lectin-Associated Serine Protease)

- Mannose-binding lectin (MBL) is a collagen-like serum protein that mediates activation of the complement system and is of importance for host defense.
- MBL in serum was associated with a serine protease named MBL-associated serine protease or MASP (MASP-1).

Trafficking of Immune Cells

- **Tethering** – p-Selectin and E-Selectin (in the epithelium) will bind their ligands present on leukocytes.
- This will slow the leukocyte down (rolling), allowing other interactions (Integrins) to occur ultimately leading to activation.
- Upon activation, cells can migrate (Extravasation) into the underlying epithelium to the sites of inflammation.

What Signals Alter the Cell Surface Expression of Selectins?

- **P-selectin** requires biochemical activation from Weibel Palade bodies (endothelium) or α-granules (platelets)
  - activated by thrombin, histamine, peroxide, ROS
  - activation peaks 10-20 min.
- **E-selectin** requires biochemical activation and are found on endothelial cells
  - recruit polymorphonuclear leukocytes, myeloid cells and T-lymphocytes
  - activated by IL-1β, TNF-α, LPS
  - response 2-24 hrs and peaks 4-6 hrs
- **L-selectin** are expressed on leukocytes
  - recruits cells to area of inflammation
  - cleaved from the plasma membrane upon activation

Glycans Play a Critical Role in Leukocyte Trafficking During Inflammation:

Leukocyte recruitment can also be promoted by endothelial-adherent platelets. In this scenario, platelets can serve as a bridge between leukocytes and the endothelium. The leukocyte/platelet interaction can be mediated by leukocyte PSGL-1 binding to P-Selectin expressed on platelets, as well as by the binding of E-2 integrin Mac-1 to its multiple ligands/counter-receptors on platelet.
The Immune System: Adaptive Immunity

Adaptive Immunity:
- Leukocyte trafficking
- The activation of B and T cells
- B and T cell signaling

The Innate and Adaptive Arms of the Immune Response Work in Concert

DCs are central players in general inflammation mechanisms.

B-Cell Physiology

Galectins differentially shape the B cell compartment by modulating B cell maturation, activation, differentiation and survival.

Binding of the pre-B cell receptor to stromal cells during development depends on anchoring to galectin 1.

Galectin 3 favors survival of B-cells and appears to mediated IL-4 induced differentiation.
Glycosylation Regulates TCR Signaling

**Glycosylation controls the threshold of TCR activation**

The GnT5 glycosyltransferase, a mannoside acetylgalactosaminyl transferase 5, initiates the formation of the 1,6 N-glycan-branch structure on various glycoproteins.

The resulting sugar is a ligand for galectins

TCR clustering is significantly increased, which coincides with a decreased threshold of T-cell activation.

Some Functions of Glycans on Fc Portion of IgGs

- Terminal Gal residues affect Complement Dependent Cytotoxicity activity of IgG molecules.
- Terminal GlcNAc residues on IgG regulates clearance.
- Absence of core fucose results in enhanced antibody-dependent cellular cytotoxicity (ADCC) activity of IgG.
- Terminal sialylation affects IgG functions - Increased serum half-life, decreased ADCC activity, both positive and negative roles in antibody functions.
- High mannose structures increase ADCC activity of IgGs & differentially regulate half-lives in serum.

Galec%ns

par%cularly glycosylated receptors (including CD22) with the BCR, thereby increasing the threshold of immune signaling and promoting endocytosis of the BCR in a CD22-dependent manner.

Loss of CD22 Siglec ligands owing to ST6Gal1 sialyltransferase deficiency markedly increases the co-localization of a possible role for these galectins in regulating central tolerance.

Galec%ns can form lattices with Complex-N-glycans to limit TCR Clustering – increasing the threshold for signaling.

Following T cell activation, galectins bind to particular glycosylated receptors (including CD3) trigger distinct intracellular events to induce T cell death.

These events are mediated in part through the developmental regulation of cell surface glycosylation.

In the thymus galectins induce apoptosis in double-negative (CD4 CD8) or double-positive (CD4 CD8+) thymocytes, suggesting a possible role for these galectins in regulating central tolerance.
• Play roles is differentiating self- and from non-self
• Mediate many pathways associated with the immune system, such as the homing of leukocytes (etc.) to sites on inflammation
• Act as physical barriers and as decoys

The extracellular secreted mucus and the cell surface glycans play numerous roles in the immune system. Many glycans play numerous roles in the immune system, leading to defects in the immune system.

Glycans as Physical Barriers and Decoys

• It multicellular organisms it’s not always possible to “change the extracellular glycans” to avoid colonization
• Glucocorticoids, such as mucins, can provide physical barriers preventing microbes from interacting closely with the plasma membrane
• In some cases these mucus layer can shed, reducing microbial load
• Soluble carbohydrates are secreted which can bind microbial glycans using proteins – thus acting as a decoy for the membrane bound glycans which are exploited for attachment and colonization

Components of your gut mucosa

Mucins and ECM

• The extracellular secreted mucus and the cell surface glycans prevent infection by the vast numbers of microorganisms that live in the healthy gut.
• From the stomach to the rectum, the mucosa consists of a single layer of columnar epithelial cells covered by a layer of secreted mucus that is at its thickest in the stomach and colon.
• Typically, anaerobic commensal microorganisms occupy only the outer mucus layer, leaving the inner mucus layer effectively sterile
• Ongoing degradation of the outer mucus layer by anaerobic bacteria means that the mucosa must be continually replaced by the epithelium.
Mucins can protect the underlying epithelium from bacterial infection

Got Milk?

- The human-milk glycans, which include oligosaccharides in their free and conjugated forms, constitute a major and innate immunologic mechanism by which human milk protects breast-fed infants against infections.
- The alpha1, 2-linked fucosylated glycans are the dominant glycan structure.
- Many of these oligosaccharides are homologs of the Lewis-secretor histo-blood group antigens.

Consumption of Milk High in Oligosaccharides is Linked to a Lower Incidence of diarrhea

In vitro and in vivo binding studies have demonstrated that alpha1,2-linked fucosylated glycans inhibit binding by campylobacter, stable toxin of enterotoxigenic Escherichia coli, and major strains of caliciviruses to their target host cell receptors.

It should be noted that some oligosaccharides in milk can also positively select for beneficial microbes.

The presence of sulfated-mucin-like proteins in your oral cavity also play a protective role.

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Glycans and Vaccines
**Viral Glycan Binding Proteins**

- Affinity of this interaction is relatively low, but the avidity for cell membranes increases because of oligomerization of the hemagglutinin into trimers.

- Binding is a prerequisite for fusion of the viral envelope with the plasma membrane and for uptake of the virus into cells.

**Host-pathogen Interactions**

- Glycans act as specific binding sites for a variety of viruses, bacteria, and parasites, and as recognition targets for many plant and bacterial toxins.

- Viruses, bacteria, and protozoa express an enormous number of glycan-binding proteins or lectins. Like the ABO blood groups, many of these proteins were isolated by hemagglutinin assays.

- The first microbial hemagglutinin identified was in the influenza virus, and it was shown by Alfred Gottschalk in the early 1950s to bind to erythrocytes and other cells through sialic acid residues of cell-surface glycoconjugates.

- Bacterial lectins also have hemagglutinating activity, but their primary function is to facilitate attachment or adherence of bacteria to host cells, a prerequisite for bacterial colonization and infection. These proteins are frequently referred to as adhesins.
Different virus subtypes have different specificity for glycans

- Human strains of influenza-A and -B viruses bind primarily to cells containing NeuSAcα2→6Gal-.
- Chicken influenza viruses bind to NeuSAcα2→3Gal-.
- Porcine strains bind to both NeuSAcα2→3Gal- and NeuSAcα2→6Gal-.
- Influenza-C virus binds exclusively to glycoproteins and glycolipids containing 9-O-acetylated N-acetylneuraminic acid.
- These linkage preferences are due to certain amino acid changes in the hemagglutinin.

Minor Mutations in HA can switch it's species specificity

A small mutation in HA can switch it from binding to bird type glycans (2-3 linked sialic acids) to human type glycans (2-6 linked sialic acids) resulting in a switch over of the virus's ability to infect humans.

Influenza desialylates target cells

- Influenza-A and -B virions express a sialidase that cleaves sialic acids from glycoconjugates. Its functions may include:
  - prevention of viral aggregation by removal of sialic acid residues from virion envelope glycoproteins
  - dissociation of newly synthesized virions inside the cell or as they bud from the cell surface
  - desialylation of soluble mucins at sites of infection in order to improve access to membrane-bound sialic acids.

Neuraminidase inhibitors can inhibit the viral life cycle

- Neuraminidase is essential requirement for the viral life cycle
  - the addition of a bulky guanidino side chain at the C-4 position of a previously known neuraminidase inhibitor, 2-deoxy-2,3-dehydro-N-acetylneuraminic acid, markedly increased the affinity for influenza neuraminidase, without having similar affects on host-cell neuraminidases.
Bacterial Adhesins

- Bacterial lectins occur commonly in the form of elongated, submicroscopic, multisubunit protein appendages.

- Most bacteria (and possibly other microorganisms) have multiple adhesins with different carbohydrate specificities, which help define the range of susceptible tissues (i.e., the microbe’s ecological niche).

The principle of bacterial adhesion as a prelude to infection

Bacterial adhesins bind to these structures:
- D-mannose (1),
- galabiose (2),
- 2-3 sialyllactose (3),
- GalNAcβ1-4Gal (4),
- D-galactose (5),
- L-fucose (6),
- Lewis b antigen (7)

Lewis Antigens are Targeted by Bacteria

- Lewis Antigens: a related set of glycans that carry α1–3/α1–4 fucose residues

- The Lewis a antigen (Lea) is synthesized by an α1–3/α1–4FucT encoded by the Lewis (Le) blood group locus.

- The Lewis b antigen (Leb) is synthesized by the concerted actions of the Lea α1–3/α1–4FucT and the α1–2FucT encoded by the Se gene.

Lewis Antigen

- H. Pylori colonizes humans and primates, primarily residing in gastric epithelial cells and mucus

- H. Pylori binds several carbohydrates including the the Lewis B antigen
E. Coli K99 binds only to glycolylneuraminic acid

_E. coli_ K99 binds to glycolipids that contain N-glycolyneuraminic acid (Neu5Gc), in the form of Neu5Gcα2–3Galβ1–4Glc, but not to those that contain N-acetyleneuraminic acid.

N-glycolyneuraminic acid is found on intestinal cells of newborn piglets, but it disappears when the animals develop and grow, and it is not formed normally by humans.

This can explain why _E. coli_ K99 can cause often lethal diarrhea in piglets but not in adult pigs or humans.


There are several toxins which are dependent on Glycans as well

- The toxin from Vibrio cholera (cholera toxin) consists of A and B sub-units in the ratio A8B5.
- This toxin binds the Galβ1–3GalNAc moiety of GM1 ganglioside receptors through CRDs located on the base of the subunits.
- Upon binding to membrane glycolipids through the B subunits, the A subunit is delivered to the interior of the cell by an unknown mechanism.

The A-subunit of Cholera Toxin is a Glycosyltransferase

- The A-subunit of Cholera toxin transferase contains an ADP-Ribosylase – which modifies and inactivates the regulatory subunit of adenylate cyclase (G-protein) leading to elevated cAMP levels.
- This disturbs the organization of the epithelium, thus benefitting the pathogens by facilitating their rapid dissemination into the environment.

Roles of Carbohydrates

Host Cell Interactions

Sialic acid residues can modulate the ability of _plasmodium_ to invade host erythrocytes. Some strains of _P. falciparum_ can reversibly switch from sialic-acid-dependent to sialic-acid-independent invasion.

Antigenic Variation

Molecular Mimicry

Viability of the protozoan

Several million people die each year from parasitic diseases, primarily from malaria and parasitic protozoans.

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Estimated human infection</th>
<th>Estimated death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasitic malaria</td>
<td>600,000,000,000</td>
<td>1,000,000,000</td>
</tr>
<tr>
<td>Parasitic sleeping sickness</td>
<td>100,000,000</td>
<td>20,000,000</td>
</tr>
<tr>
<td>Parasitic Trypanosomiasis</td>
<td>500,000,000</td>
<td>100,000</td>
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<tr>
<td>Parasitic typhoid fever</td>
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<tr>
<td>Parasitic kalaazar</td>
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Glycans and Vaccines

Molecular Mimicry

- Group A Streptococcus (GAS) expresses a nonimmunogenic capsule of hyaluronan, identical to the nonsulfated glycosaminoglycan abundant in host skin and cartilage

Natural selection has favored microbes which have developed a range of strategies to subvert the mucin barrier

- Degradation of mucus
- Avoidance of mucus
- Alteration in host cells

The Clostridium novyi toxin transfers a GlcNAc residue to Rho

- Clostridium novyi is involved in toxic shock and gangrene.
- Clostridium difficile causes pseudomembranous colitis
- The toxins of Clostridium inactivate Rho/Ras proteins by glucosylation or attachment of GlcNAc

Structure and mode of action of clostridial glucosylating toxins: the ABCD model


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Molecular Mimicry – Sialic Acid

- Neither N-acetylneuraminic acid (Neu5Ac), the most common sialic acid, nor any of its >50 structural derivatives is synthesized by most plants, lower metazoa, protists, Archaea or Bacteria.

- Since its discovery in 1959 in the culture supernatant of Escherichia coli K1, sialic acid has been detected in a growing list of other bacterial, fungal and protozoan species.

- In each case, sialic acid is thought to function as an anti-recognition molecule by allowing the sialylated microorganism to maskerade as "self" while eluding host immune mechanisms that would otherwise rapidly clear an unsialylated strain.

Where Does the Sialic Acid Come From?

Table 1. Summary of microbial sialic acid metabolism

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Neuraminidase</th>
<th>Synthetase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria meningitidis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>E. coli K1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- De novo biosynthesis (convergent evolution)
  - Neisseria meningitidis & E. coli K1

- Donor scavenging
  - Neisseria gonorrhoeae
  - Uses CMP-Neu5Ac in host secretions

- Precursor scavenging
  - Haemophilus influenzae can catabolise free sialic acid

- Trans-Sialidase
  - Trypanosomes

Trans-sialidase: Trypanosome steal it!

- Trypanosoma cruzi has developed an interesting strategy of molecular camouflage in which a parasite-encoded, trans-sialidase, transfers sialic acid from serum glycoproteins in the host to membrane proteins on its own surface.

Antigenic Variation

- VSGs are dimeric proteins, consisting of two 55-kD monomers, each of which carries N-linked allogomannose-type oligosaccharides.

- As parasites multiply in the host bloodstream, the host immune system mounts an immune response that is effective against only a certain population of trypanosomes, those expressing the antigenic VSG.

- Those that have switched to an alternative VSG coat (encoded among 1000 distinct VSG genes) escape immunological destruction.
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**Glycans and Vaccines**


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The AIDS virus coat protein (Env) is amongst the most heavily glycosylated proteins known. As with many viruses, the glycans serve to mask the virus from the host immune system since the glycans are assembled via the host glycosylation machinery.

Glycans on Env are essential for its folding and they play a role in its binding to and uptake by host cells.

The variability and changes in the glycans on the Env glycoprotein of AIDS virus during disease progression and on different virus strains is one of the major roadblocks to vaccine development.

**Immune Responses to Sugars**

- Vaccines consisting solely of glycan components typically elicit poor immunity
- The primary limitation is that glycans are T-cell-independent antigens and therefore do not effectively stimulate T-helper-dependent activation and class switching of B-cell-mediated immunity.
- Conjugate vaccines with oligosaccharides coupled to carrier proteins have proven to be highly effective.

[http://www.case.edu/med/pathology/faculty/cobb/lab/Research.html](http://www.case.edu/med/pathology/faculty/cobb/lab/Research.html)

[One Mechanisms of CD4 independent Transmission of HIV Relies on Carbohydrates](http://www.case.edu/med/pathology/faculty/cobb/lab/Research.html)

Inspite of the fact that Carbohydrates Often Make Poor Antigens, Many Vaccines are Directed Against Carbohydrates:
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