Glycan-Pathogen Interactions Lecture 15

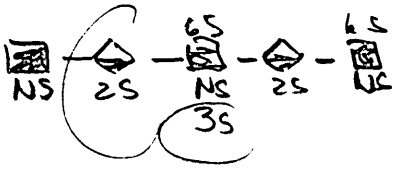
- A variety of viral, bacterial and parasitic pathogens express adhesins that bind to host glycans (receptors)
- Bacteria also produce toxins that bind to glycans
- Adhesins often are hemagglutinins

Viruses

- Flu encodes a hemagglutin (H) and a neuraminidase (N)
  - H has low affinity for sialic acid → trimers → avidity (also high density of ligands)
  - Influenza A+B (Human) NeuAcα2,6 Gal, expressed on tracheal epithelial cells
  - Avian strains - specific for NeuAcα2,3 Gal (Slide 1)
  - Influenza C - 9-O-acetyl NeuAc
  - H is major antigen - rapidly mutates
- Neuraminidase
  - prevents viral aggregation, virus-cell attachment during virus release, removal of mucin sia which acts as a decoy
- Many other viruses use Sia - rotavirus, Sendai, Polyoma, others
- Dengue (Zika), HIV, HSV use heparan sulfate

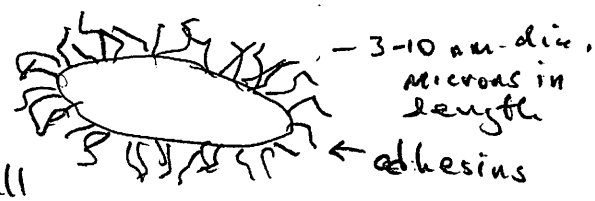
(Slide 2)

- HSV expresses gB and gC that bind HS, then gD engages 3-O-sulfated HS ("gD-type HS3Sts) and binds to fusion receptors (HVEM family)



Bacteria

Slide 3



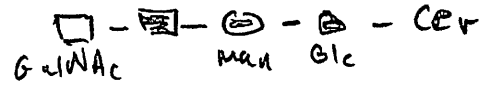
- fimbrae / pili
  protein threads - actually covalently linked to cell wall
- bind to glycoproteins and GSLs
  - FimH on E. Coli binds α-mannose - example of a catch-bond; resists shear forces

Toxins

- cholera toxin AB_5 - binds to GM_1, induces endocytosis → retrograde transport → retrotranslocation of A_1 subunit and ADP-ribosylates G proteins

Slide 4

- Bacillus thuringiensis - produce crystal toxins (Cry proteins, δ-endotoxin); binds to insect specific GSL



- proteolytically processed → pore forming, gut paralytic

Parasites

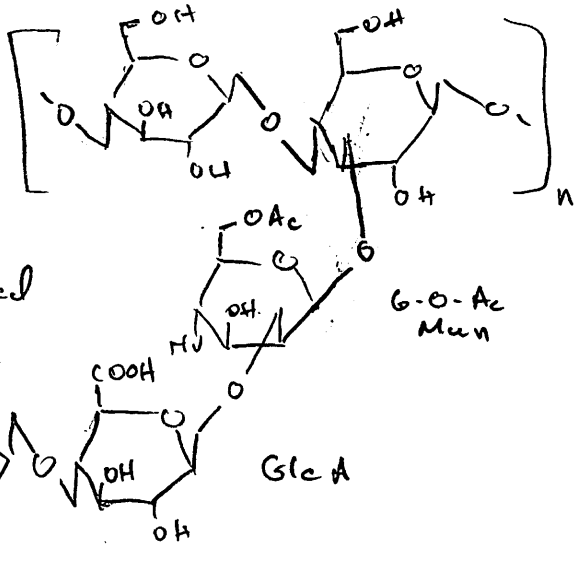
- Many parasites use adhesins to bind to cells
- Entamoeba - Gal/GalNAc
- Plasmodium falciparum (malaria) -
  - Sporozoite (insect) infects host, circumsporozoite protein binds to HS in hepatocytes and invades
  - Merozoites bind to sialic acid on RBC, glycophorin

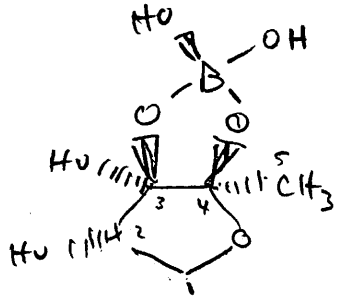
Anti-adhesion therapy - discuss how one might design therapeutic agents

Commensal bacteria - benefit of bacteria without harming host
Symbiotic - mutually beneficial (Rhizobium)
Pathogenic - benefit to bacterium - harms the host

- Bacteroides thetaiotaomicron - anaerobic symbiont
  - Gnotobiotic mice do not express fucosylated glycans on intestinal epithelium
  - Inoculate with B. theta → Fuc α1,2 expression is induced by bacteria protein; B. theta expressed fucosidase and fucose permease
  - Foraging

- Biofilms - polymicrobial communities, eg. oral plaque but also found throughout nature (ponds, ships ...)
  - Extracellular (EPS) polysaccharides (capsular components) forms matrix that allows bacteria to colonize; polyuronides modified with sulfate, phosphate, O-acetyl, pyruvate, etc
  - quorum sensing - furanosyl borate diesters, acyl homoserine lactones, others accumulate and activates maturation and disassembly of EPS
  - Phytopathogen Xanthomonas campestris - infection creates an EPS containing xanthan gum, which blocks waterflow in plants → wilting - the physical properties of xanthan gum makes it a food additive eg. thickening agent

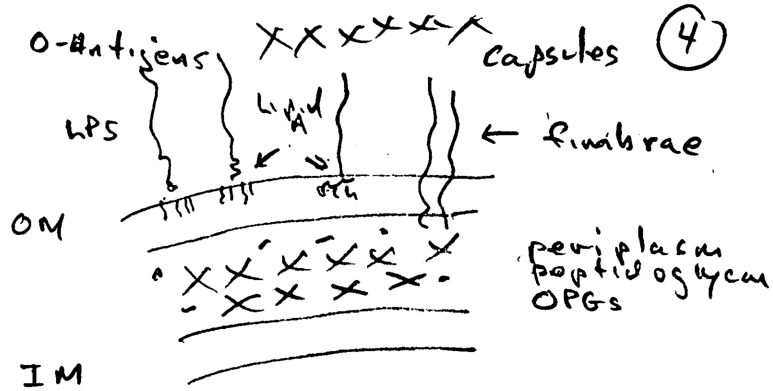




from 1-deoxy-3-dehydro ribulose

Bacterial Glycans

Slide 5 and 6

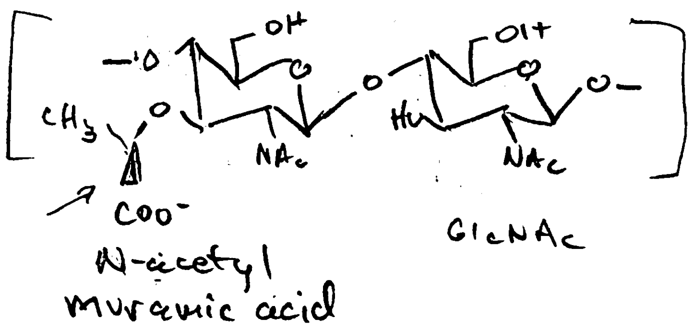


Gram staining
- Gm⁻ have OM and LPS
- Gm⁺ lack OM, contain thicker peptidoglycan and teichoic acids

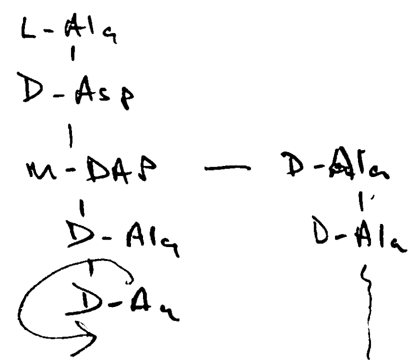
Peptidglycan

- 10% of dry wt of gm neg., 1-3 layers thick, 25-35 disaccharides

Slide 7



Amino acid licases assembles pentapeptide



- 25% of dry weight in gm⁺ 10-20 layers, ~100 disaccharides
- ~50% turnover per generation due to expansion and cell division (septation)

Assembly

cytosolic side of inner membrane:

UDP-GlcNAc + PEP → UDP-MurNAc → UDP-□ $(aa)_5$

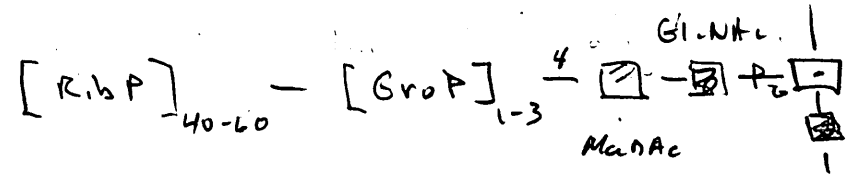
Lipid II-P-P-□-■ (aa_5) ← (UDP-■) ← Lipid I-P-P-□ $(aa)_5$ ← C55 bactoprenol

flips → glycosyltransferase

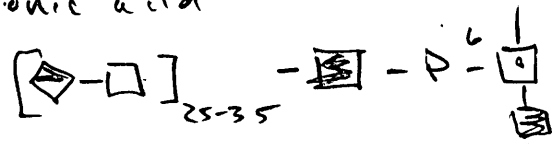
→ Lipid II-P-P-□-■-□-■ (aa_5, aa_5) → transfer to existing peptidoglycan by transpeptidases

Gram positive teichoic acids

- Wall TAs - polyribitol - polyglycerol (40-60 repeats) linked to C6 of MurNAc



- Teichuronic acid



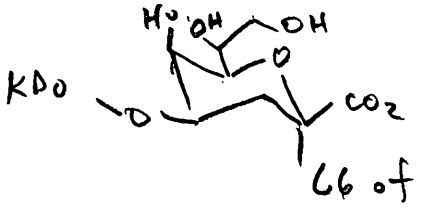
- Lipid teichoic acids linked by way of diglyceride

Lipopolysaccharide — LPS - Heat stable toxin

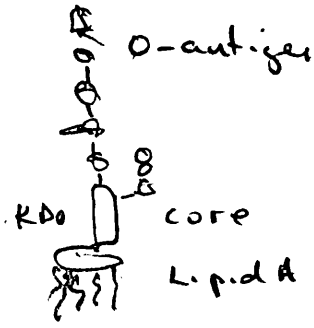
Slide 9

- low levels of LPS stimulate the adaptive immune response by activating monocytes and macrophages to produce T/B cell active cytokines
- Mono phospho lipid A is licensed adjuvant (Cl-P gone)
- High levels of LPS → septic shock

- Core oligosaccharide consists of 1-4 KDO



+ other sugars



- O-antigens
  - >180 types in E. Coli
  - basis for serotyping bacteria
  - consists of repeat units of 1-8 sugars

Assembly occurs in periplasmic space (think EE) and transfered to Lipid A and then translocates across periplasm to outer leaflet of outer membrane

Capsules K antigens

- huge diversity
- mucoid appearance
- protects against dessication, bacteriophages
- virulence factor - blocks complement
- vaccine candidate
- molecular mimicry
  - HA (GAS), Sia-LacNAc (GBS), PSA (Neisseria)
  - GAGs (E. Coli and Pasturella)

N-linked

- uses bactoprenol - very similar to eukaryotic system in terms of assembly, sequon, and transfer but oligosaccharides are shorter and homogeneous
- no processing
- also generates ≤ 2.5% of dry weight of free oligosaccharides

Osmoregulated Periplasmic Glucans

- ✓ 5-12 glucose units, β1,2 with β1,6 branches
- ✓ can be decorated with glycerol (P) derived from phosphatidylglycerol
- ✓ induced by osmotic conditions
- ✓ can represent a few percent of dry weight