Bacterial Pathogenesis

How do bacteria cause disease?

Which bacteria cause disease?

Commensal flora - oral streptococci

Pathogens - Group A Streptococcus
  Pharyngitis
  Impetigo
  Rheumatic disease - secondary to immune response to the organism - cross reactive Abs

Commensal flora - *E. coli* - acquire virulence genes

*E. coli* -0157:H7 - toxigenic - hemolytic uremic syndrome
Or is it the host response to the bacteria?

Depends upon the host:
- Coagulase negative Staphylococci - skin flora
  Colonize catheters, prosthetic devices, neonates

Location of the organism:
- Invasion into a normally sterile site:
  - S. aureus on the skin - colonization
  - bloodstream - bacteremia/sepsis

Or is it the host response to the bacteria?

- The anterior nares is the primary site of colonization
- Colonization occurs in 20-40% of "normals"
- Infections are increased in colonized subjects usually with the colonizing strain
  - Colonization increased in IVDU, diabetics, HIV-infected
  - Elimination of carriage in high risk patients has been shown to reduce infection rates
- Most infections result from autoinoculation
  - 82-86% of cases S. aureus bacteremias (Von Eiff et al., 2001)
5 fold increase in pediatric influenza associated deaths 2006-07 due to S. aureus bacteremia/pneumonia

- Of the 22 deaths associated with S. aureus, 15 were caused by MRSA
- Similar data reported by Hageman et al. 2003-2004 influenza season
How do bacteria cause disease?

1 - Attachment

2 - Toxin expression

3 - Direct damage

4 - Activate host genes to cause damage
   - avoid immune recognition
   - look like the host
**E. coli**

- tightly adherent
- type III toxin secretion

- bacteria
- mucin
- microvilli
**Bacterial life styles**

Extracellular - Environment → Host

- Relatively hardy - resistant to extremes in temperature, can deal with various growth conditions - not fussy
- some extracellular also are well adapted to live intracellularly - *Shigella*

Intracellular organisms (obligate) - *Chlamydia*

- Predominantly intracellular - highly adapted to live within a macrophage - *Salmonella, Mycobacteria tuberculosis*
How do bacteria “sense” the environment?

- extracellular versus intracellular temperature, phosphate, glucose, magnesium etc.

Two component signal transduction

SENSOR COMPONENT - phosphorylation

Response regulator

Coordinate regulation of virulence genes

In response to a given environmental signal

Two component signaling

Coordinate regulation of virulence genes

In response to a given environmental signal
**Salmonella invading a gut epithelial cell**

**Salmonella adaptation**

- phoP/phoQ - 2 component signaling
divalent cations

Changes in LPS

Affects susceptibility to antimicrobial peptides
And antigenicity

Intracellular - T cell recognition for clearance
Pathogenesis of Salmonella infection

Enteritis

- Ingestion
- Peyer's patch
- Macrophage
- Neutrophils
- T cells
- Dendritic cell
- MLN
- Hepatic bone marrow
- Liver
- Kidney
- Blood

Enteric Fever

- Enterocyte
- M = M cell
- N = Neutrophil
- Mo = Macrophage
- S = Salmonella

1. Basal migration of enterocytes
2. Perturbation of membrane and ingestion
3. Migration of enterocytes
4. Epithelial cell-to-cell secretion
5. Survival in macrophages

Migration of infected macrophages to lymphoid and peripheral organs via lymphatics and blood.

Vinorelbine

References:
- SR1 TTS\c\n- mAb1 TTS\c\n- mAb2 autocatalytic entry
**Bacterial virulence factors**

*What is a virulence factor?*

1. Facilitate colonization – fimbriae, pili
2. Thwart immune response – capsule, IgG binding
3. Directly damage host tissues

*Streptococcus pyogenes* – Group A Strep

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**GROUP A STREPTOCOCCAL VIRULENCE FACTORS**

- Adherence
- Internalization
- Invasion
- Anti-phagocytic activity
- Lipoteichoic Acid
- Fibrinogen-Collagen-Binding Proteins
- Capsule
- M Protein
- Exotoxins
- Pyrogenic Toxins
- Superantigens
- Proteases
- Streptokinase
- DNases

**Systemic Toxicity**

**Dissemination**

**CELL AND TISSUE LEVEL**

**ORGANISM LEVEL**
TOXINS

- Modify host components - ADP ribosylating enzymes
- Activate the cells - cytokine expression
- Alter tight junctions - allows invasion
- Stop protein synthesis
- Activate secretory systems - adenyl cyclase
  - *Vibrio cholera*
- Induce apoptosis - airway epithelium – *Pertussis*
- Stop protein synthesis
Toxins - Recognize eukaryotic receptors

Cholera toxin
  Activates Chloride (and H₂O) secretion
  Via cAMP activation

Clostridium botulinum toxin - motor end plates
  Spores - resistant to sterilization
  Soil contaminants

  Organic honey - infants ingest organisms -
  Grows - produces toxin -
  Become floppy, lethargic -
  Infant botulism
Infant botulism

Toxin prevents acetylcholine release
Activation of host immune signaling

Innate immune responses

Toll like receptors and many others

Activation of TLRs -
Conserved signaling cascades
Initiate inflammation

TLR polymorphisms -
Genetic effects on disease susceptibility
Gram-negative bacterial endotoxin (lipopolysaccharide, LPS)

- O-specific polysaccharide chain
- Core glycolipid
- Lipid A
- (outer) (inner) core oligosaccharide
Toll like receptors

- activating an innate immune response

Pattern recognition receptors

Immuno-reactivity of shared bacterial components

Innate immune response

If disordered - ? Role in autoimmune diseases
inflammatory bowel disease
**TLR4 polymorphisms**


TLR4 polymorphisms, infectious diseases, and evolutionary pressure during migration of modern humans.


Department of Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

Polymorphisms in Toll-like receptor 4 (TLR4) have been related to susceptibility to Gram-negative infections and septic shock. Here we show that two polymorphisms of TLR4, Asp299Gly and Thr399Ile, have unique distributions in populations from Africa, Asia, and Europe. Asp299Gly has evolved as a protective allele against malaria, explaining its high prevalence in sub Saharan Africa. However, the same allele could have been disadvantageous after migration of modern humans into Eurasia, putatively because of increased susceptibility to severe bacterial infections. In contrast, the Asp299Gly allele, when present in co-segregation with Thr399Ile to form the Asp299Gly/Thr399Ile haplotype, shows selective neutrality.

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**Flagella**

Motility - swim toward a desired carbohydrate

Ligands - for mucins

clearance

Ligand for macrophages -
**Human airway cells**

- **Flagella**
- **TLR5**
- **Merge**

Airway - superficial stimulus is sufficient to activate inflammation
Apical display of the toll-like receptors

Mutations in TLRs - associated with increased susceptibility to specific bacterial infections

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**PA1244 - wild type**  
**DB103 - mutant (lacks flagella)**

Analysis of these pathways – Identify mutants
**TLR5 Polymorphisms**


A common dominant TLR5 stop codon polymorphism abolishes flagellin signaling and is associated with susceptibility to legionnaires’ disease.


Institute for Systems Biology, 1441 N. 34th St., Seattle, WA 98103, USA.

We show that a common stop codon polymorphism in the ligand-binding domain of TLR5 (TLR5392STOP) is unable to mediate flagellin signaling, acts in a dominant fashion, and is associated with susceptibility to pneumonia caused by *Legionella pneumophila*, a flagellated bacterium.

**Opportunistic pathogens**

*Pseudomonas aeruginosa*

- Genetically versatile bacteria
- Few growth requirements
- Rarely pathogenic in the normal host

- Major pathogens in immunocompromised patients
- Special settings - cystic fibrosis

Genomic sequencing - compare genetic organization of pathogens and non-pathogens
Virulence factors - *Pseudomonas aeruginosa*

1 - Turn on one group of genes in response to the environment to **ESTABLISH** an infection

- Flagella - motility
  - immune activation

- Hemolysins - Phospholipases - cleave host components

- Proteases -

- Siderophores - pigments - scavenge iron

2 - Persistence - turn ON genes to adapt to host immune response