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

S. aureus - Epidemiology

• 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
  - 22-44% of cases S. aureus bacteremia
  (Von Eiff et al., 2001)

This is an official CDC HEALTH ADVISORY

Influenza-Associated Pediatric Mortality and Staphylococcus aureus co-infection

• 5 fold increase in pediatric influenza associated deaths 2006-07 due 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

**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

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

Two component signaling
Coordinate regulation of virulence genes
In response to a given environmental signal

Salmonella invading a gut epithelial cell

Salmonella adaptation
Pathogenesis of Salmonella infection
**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

**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 cholerae*
- 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

**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

**Toll like receptors - pattern recognition receptors**

Infant botulism

Toxin prevents acetylcholine release
LPS

Peptidoglycan
Cytoplasmic membrane

How do commensal flora cause disease?

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.

Toll like receptors

- activating an innate immune response

Flagella

Motility - swim toward a desired carbohydrate Ligands - for mucins

Ligand for macrophages -
Flagella

Electron micrograph

PA1244 - wild type
DB103 - mutant (lacks flagella)

Analysis of these pathways – Identify mutants

Flagella

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.

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

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

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