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INTRODUCTION TO BACTERIOLOGY

August 22 - ?

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BACTERIA (prokaryotes) VS. EUKARYOTES

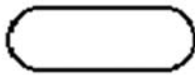
	<u>Bacteria</u>	<u>Eukaryotic</u>
Cell Structure: Organization	Unicellular	Unicellular/Multicellular
Cell Membrane:	transport, motility, oxidative phosphorylation, DNA replication	transport
Endocytosis/Exocytosis	-	+
Intracellular Membranes: (Nucleus, Golgi, Mitochondria, Endoplasmic Reticulum)	-	+
Cytoskeletal:		
Microfilaments	-	+
Microtubules	-	+
Cell wall	Peptidoglycan	-
Genetics:		
Chromosomes	1 (2: Vibrios, Neisseria)	>1
Topology	Circular	Linear
Segregation	Cell membrane coupled in cytoplasm	Mitotic spindle
Transcription/ Translation	-	Transcription - nucleus Translation - cytoplasm
mRNA capping, poly-A	-	+
Introns	(-)	+
Cistron structure	Mono + Polycistronic	Monocistronic
Ribosome	70S (50S + 30S)	80S (60S + 40S)
Genetic Exchange	Transformation, Transduction, Conjugation	Meiosis, Zygote fusion

Bacterial structure

- **Small (1-8 microns)**
- **Shapes** (important for identification and making diagnosis)



COCCUS



ROD
[BACILLUS]



SPIROCHETE

Others (**vibrios, filamentous, coccobacilli**)

Envelope structure is unique to prokaryotes

Cell wall

- rigid structure surrounding the cell membrane

Functions:

- prevent osmotic lysis
- protect cell from external stresses (host)
- contributes to virulence
- target for antimicrobials

Gram stain

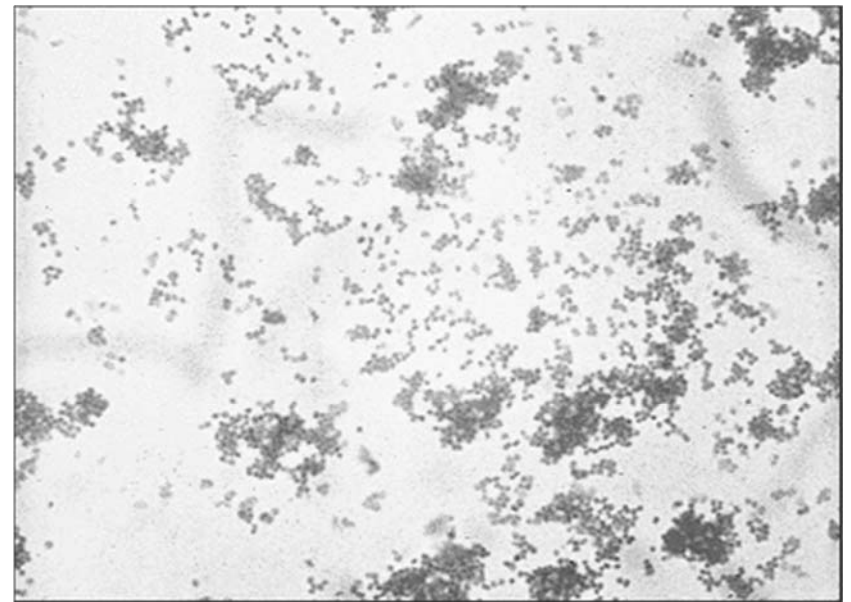
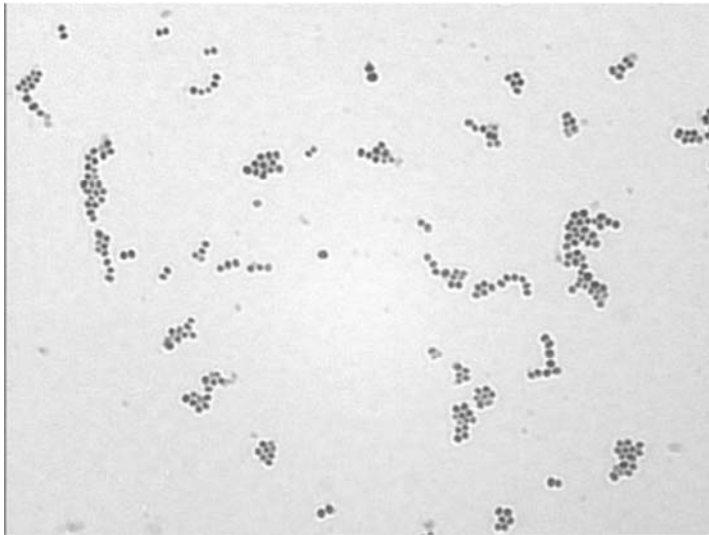
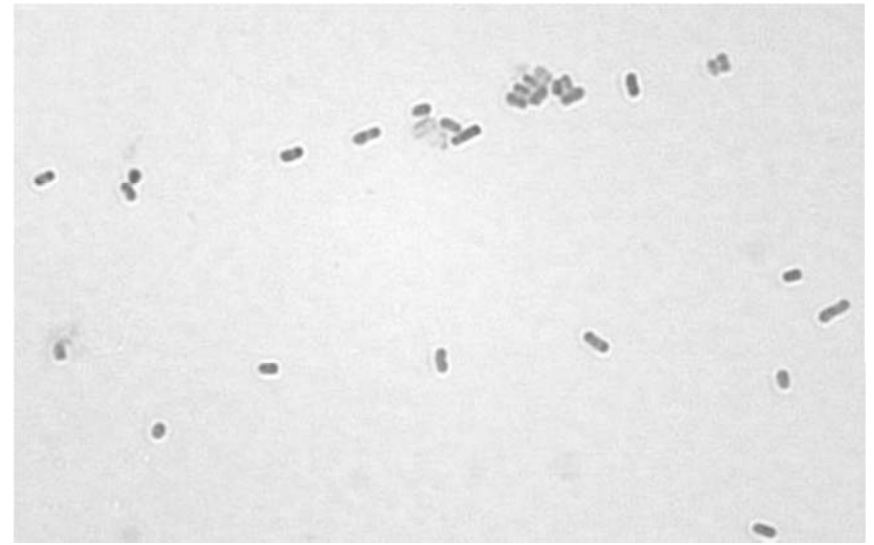
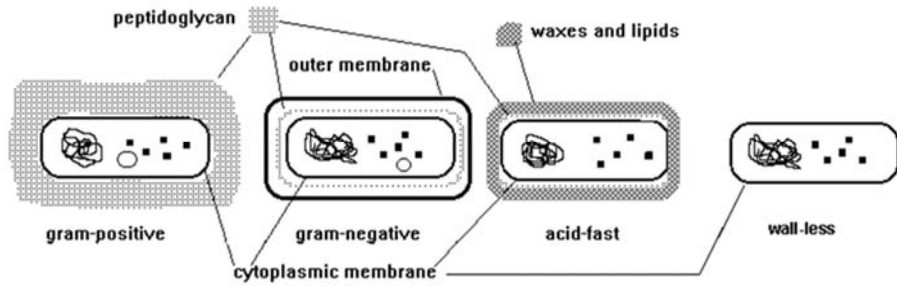
- gram-positive (blue)
- gram-negative (pink)

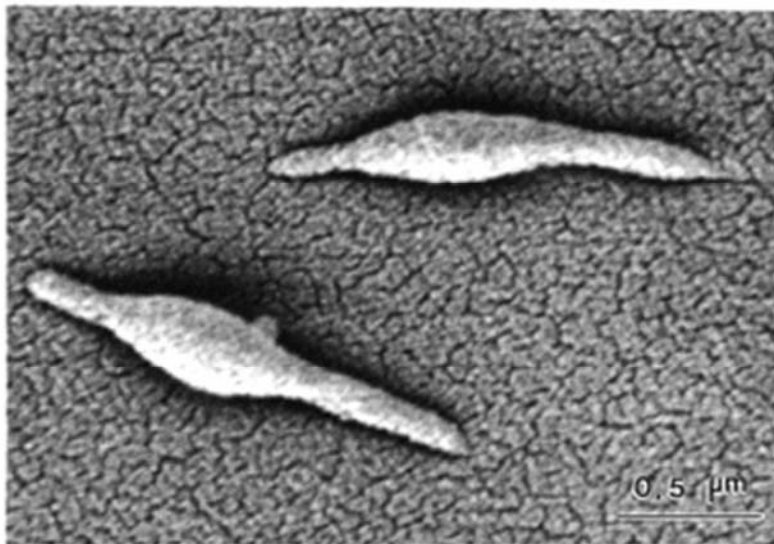
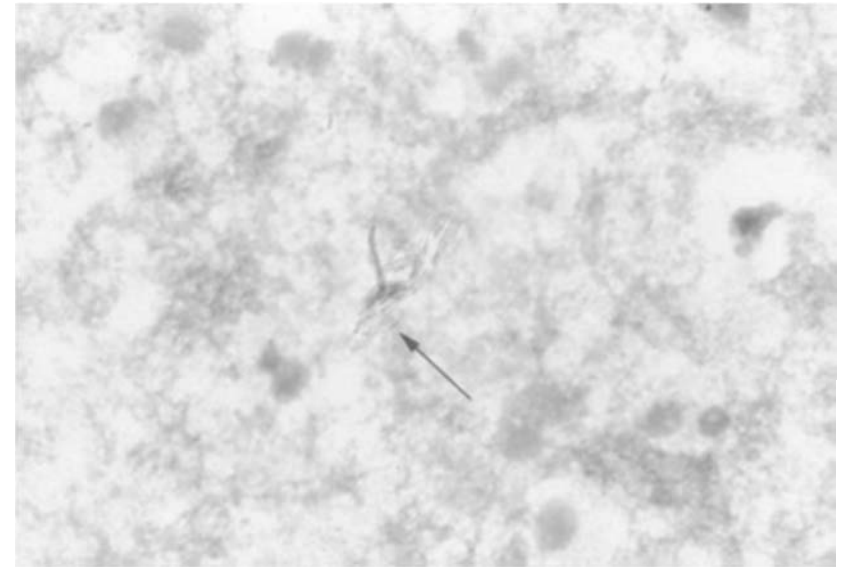
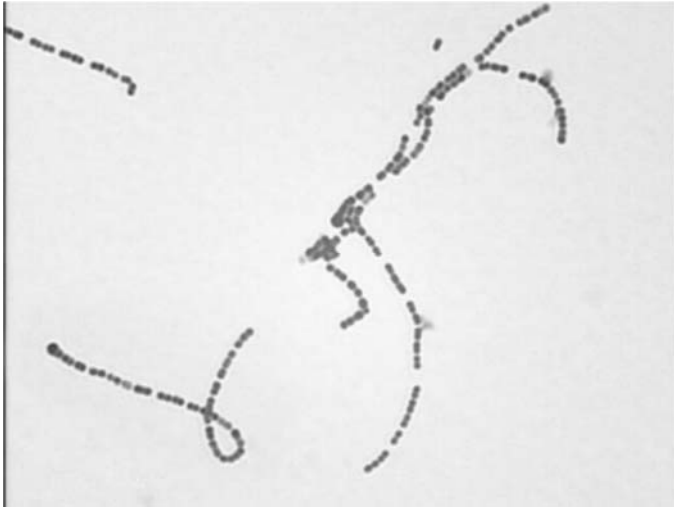
Acid fast stain

- acid fast (red on blue)

Wall-less

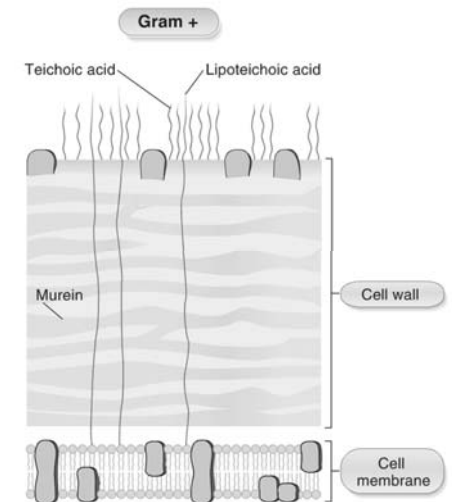
- doesn't stain - need special stain



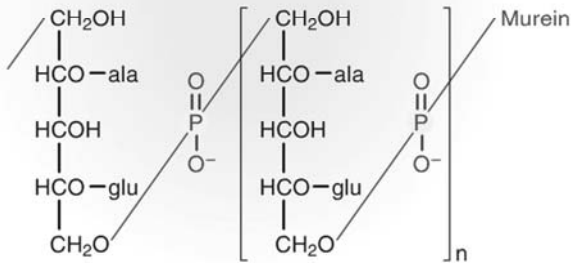
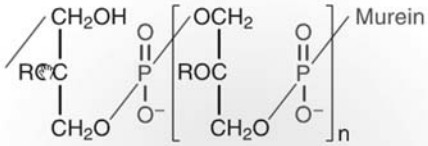


Gram-positive structure

- **thick peptidoglycan** cell wall (40+ layers of chain link fence)
- resist lysis by complement, but still can be opsonized
- **teichoic acids and lipoteichoic acids**
- other proteins and carbohydrates (fibrillar layer, carbohydrate capsule).



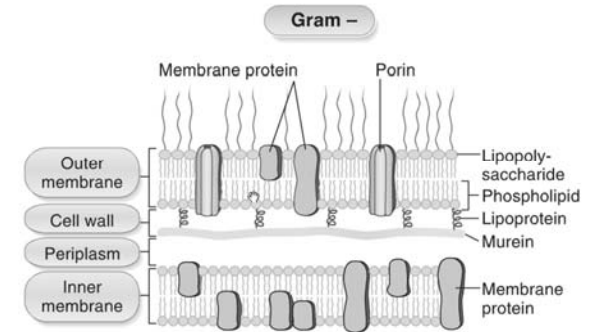
Teichoic acid



**Ribitol or
glycerol
phosphate
+
side chains**

Gram-negative structure

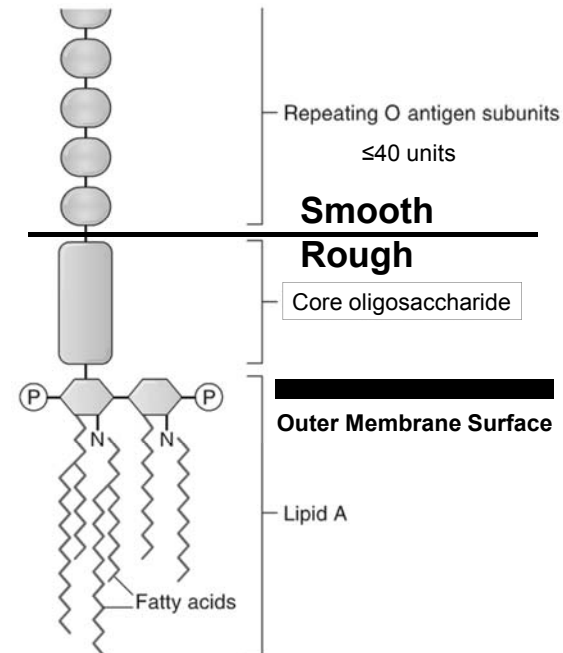
- **outer membrane** - a second lipid bilayer
- **periplasmic space** between inner (cytoplasmic) and outer membrane
- **single layer of peptidoglycan** in periplasmic space
- **porins** enable diffusion across outer membrane
- outer surface - **lipopolysaccharide (LPS)**, important in pathogenesis
- Targeted by **polymyxins**



Lipopolysaccharide (LPS) – Endotoxin

The most important part of gram-negative bacteria

- **lipid A**
 - embedded in membrane = **endotoxin activity**
 - unique C14 fatty acid - **β -hydroxy myristic acid**, phosphates, glucosamine
 - **recognized by TLR4**
- **core oligosaccharide**
 - highly conserved among different bacteria
 - unique components - **KDO and heptose**



**LPS
Structure**

- **O antigen**
 - may be present or not, depending on species
- **repeating units** of 3 to 5 sugars
- **smooth** with O antigen
- **rough** without (ending at core)
- LPS of bacteria without O antigen sometimes called lipooligosaccharide (LOS)
- **antigenic** and highly **variable** among species and strains

Acid fast structure - (Mycobacteria)

- most similar to gram-positive bacteria
- cell wall composed of **fatty acids** and **waxes** which contribute to virulence
- hydrophobic components difficult to stain, but once stained, retain stain (resistant to acid decolorization)
- **mycolic acid, Wax D, cord factor, arabinogalactans, and sulfolipids** (mycobacterial virulence factors)

Wall-less structure - (Mycoplasma)

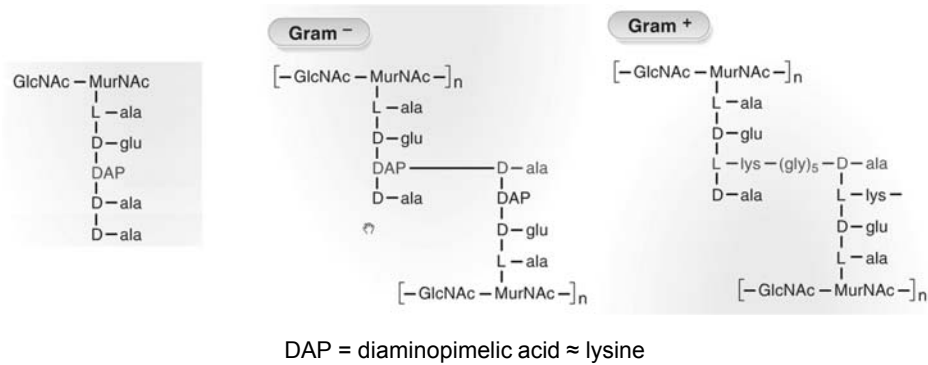
- **No cell wall (no peptidoglycan)**
- **No outer membrane**
- **Incorporation of cholesterol from host**
- **Very labile**
- **No definite shape**
- **Small genome**
- **Simplest free-living organisms (artificial life?)**

Peptidoglycan (murein layer)

- **unique to prokaryotes**
- **antimicrobials:**
 - β -lactams: penicillins and cephalosporins, vancomycin, bacitracin
- enzyme **lysozyme** hydrolyses backbone
- **composition - murein backbone with unusual peptide chain**
 - N-acetyl glucosamine - N-acetyl muramic acid
 - pentapeptide with L and D amino acids

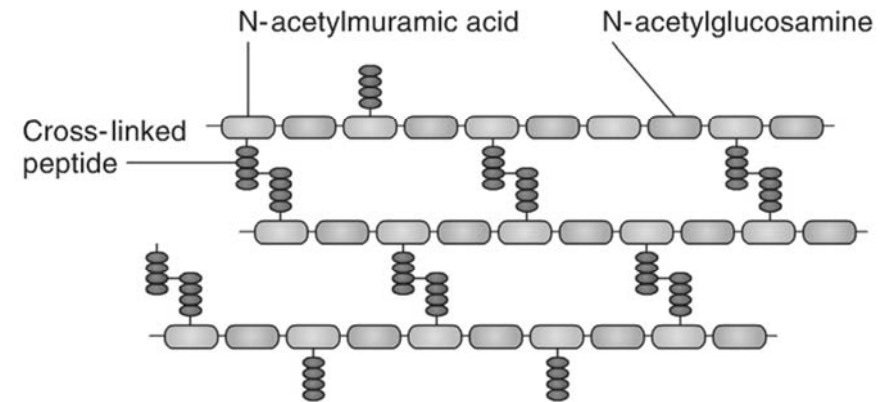
Peptidoglycan

Building blocks, Backbone polymerization, and Crosslinking



Peptidoglycan

Overall Structure

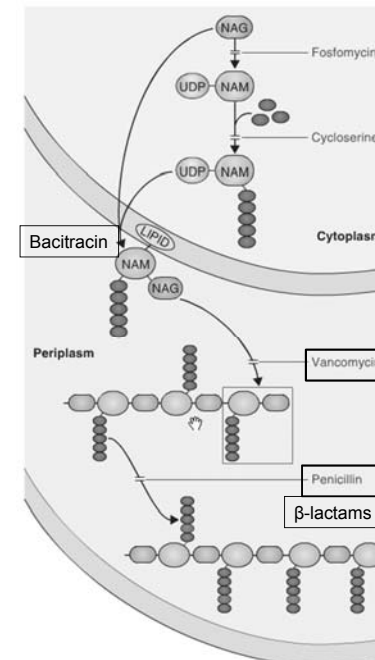


synthesis

- build blocks in cytoplasm
- **transport through cytoplasmic membrane**
 - (bacitracin-sensitive)
- polymerize backbone
- **cross-link peptides**
- **third amino acid** - NH₂ side chain (**lysine** [gram-positives] or **diaminopimelic acid** [gram-negatives]) peptide bond displaces terminal amino acid (D-alanine) of adjacent peptide chain, crosslinking chains and conferring rigidity

Peptidoglycan

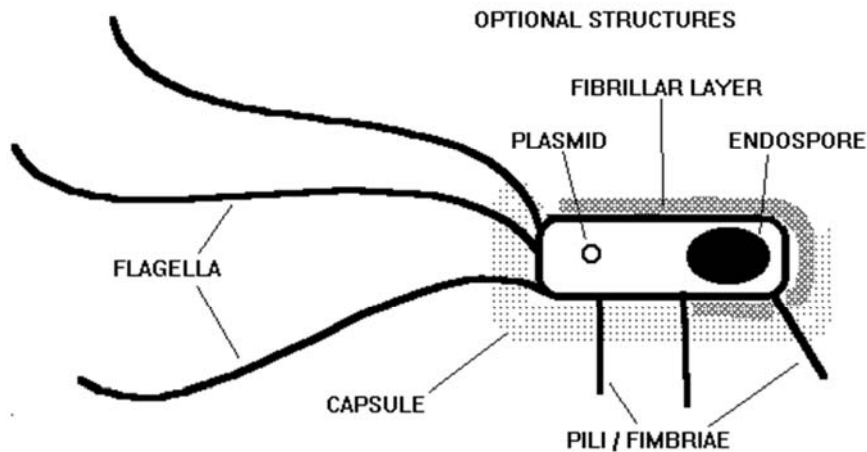
Synthesis and Transport and Antibiotics



- **Penicillin-binding proteins (PBPs)** - perform crosslinking, etc.
- some gram-positive cells - **pentaglycine bridge** to form cross-links
- **muramyl dipeptide** - highly **inflammatory** and chemotactic
- **recognized by TLR-2**

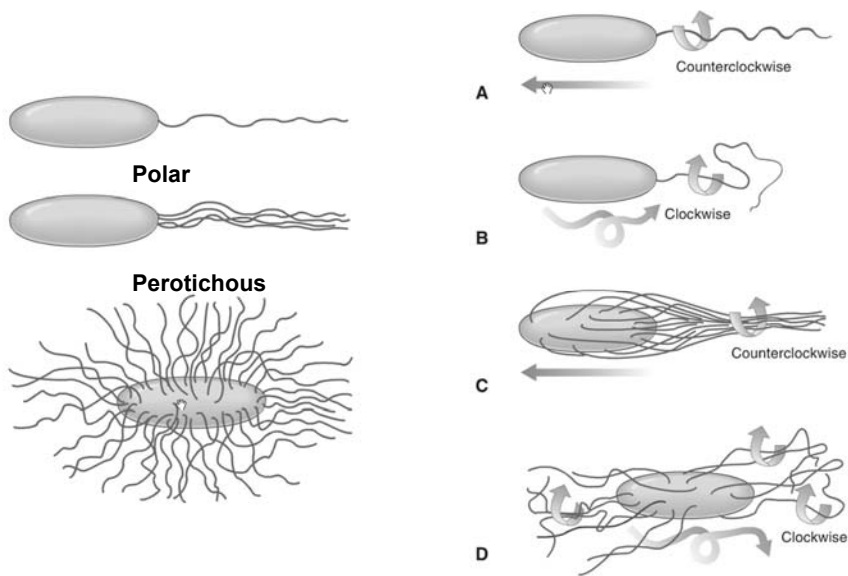
Other optional gross structural components

- **Capsule** (slime layer), K antigen
 - not impermeable
 - Both gram-positive and gram-negative bacteria can make capsules
- **polysaccharide**
 - (exception: *Bacillus anthracis* (anthrax) poly-glutamate)
- **virulence - inhibit complement - phagocytosis**
- **glycocalyx** - extracellular polysaccharide; **biofilms**; technically not a capsule



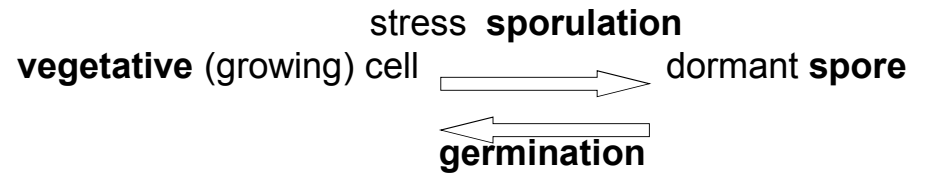
- **Flagella** - H antigen
 - propeller
 - motility and chemotaxis
 - recognized by TLR5
- **Pili/fimbriae**
 - hair-like; protein; 2 unrelated functions:
 - **adherence**
 - **genetic exchange** (not related to adherence fimbriae)
- **Fibrillar layer**
 - protein coat on surface
 - virulence (e.g., M protein of *Streptococcus pyogenes* is anti-phagocytic, others involved in adherence to host cells)

Flagella and Motility



Spores

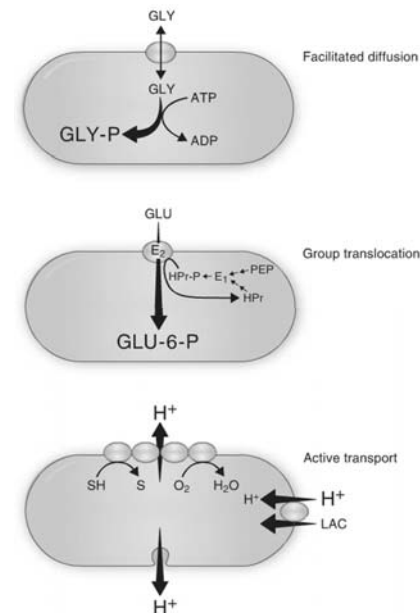
- certain **gram-positives only** - both aerobic and anaerobic
- metabolically **inactive**
- **resistant to heat (boiling), desiccation**
- contain **dipicolinic acid**
- developmental stage in response to stress:



Cytoplasmic/Inner Membrane

- **similar** to eukaryotic **plasma membrane** and **mitochondrial membrane**
- **little usefulness as target for antibiotics**
- carries out **many functions**
 - **transport:** facilitated diffusion, active transport, group translocation (phosphotransferase – carbos)
 - **electron transport and oxidative phosphorylation**
 - **energy production**
 - **motility**
 - **replication**

Transport



Nucleoid - Chromosome – DNA

- **Single, circular structure (haploid genome)**
 - **Vibrios have 2 different chromosomes**
- < eukaryotic chromosomes, ~ 3,500 genes
- **Not in nucleus - no nuclear membrane.**
Transcription in cytoplasm with translation
- **Supercoiling - DNA gyrase - DNA replication**
 - **Nalidixic acid** and other **quinolones** inhibit gyrase and DNA replication
 - **Metronidazole** – incorporated into DNA after reduction by anaerobes, inhibiting DNA replication

Metabolism

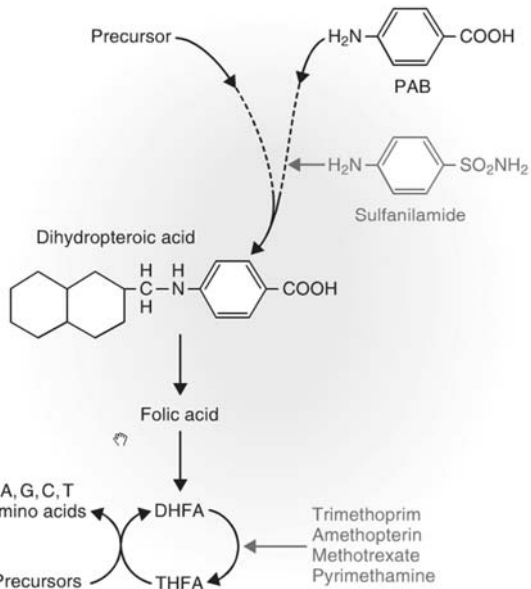
- **The "meaning of life" for bacteria is growth = replication** - they don't just sit around
- Colony Forming Unit (CFU)
- Replication = synthesizing a bacterial cell
- Most **metabolic pathways** are similar if not identical to ours, therefore not targeted by antibiotics

Oxygen and bacterial physiology and growth

- **aerobes** - grow well in the presence of oxygen; they tolerate oxygen and oxidative products of metabolism
 - **strict or obligate aerobes** require oxygen
 - **facultative anaerobes** - grow well in presence or absence of oxygen (aerobes)
- **anaerobes** - grow best in the absence of oxygen
 - **microaerophilic** or **aerotolerant** - tolerate ↓oxygen
 - **obligate anaerobes** - cannot tolerate oxygen or oxidative products of metabolism

Unique functions

- acquisition of **iron** by **siderophores** - important for **virulence**, (no antibiotics yet)
- **folic acid metabolism** (1 carbon donor: DNA synthesis, etc.)
 - **humans** get folic acid as a **nutrient**
 - **bacteria** must **synthesize**
 - **sulfanilamide** is a **PABA** analog that inhibits **dihydropteroate synthetase**
 - **trimethoprim** inhibits **dihydrofolate reductase**



Folic Acid and Antibiotics

FIGURE 5-2 ■ Inhibition of folic acid synthesis (by sulfa) and function (by other antibacterial drugs). The

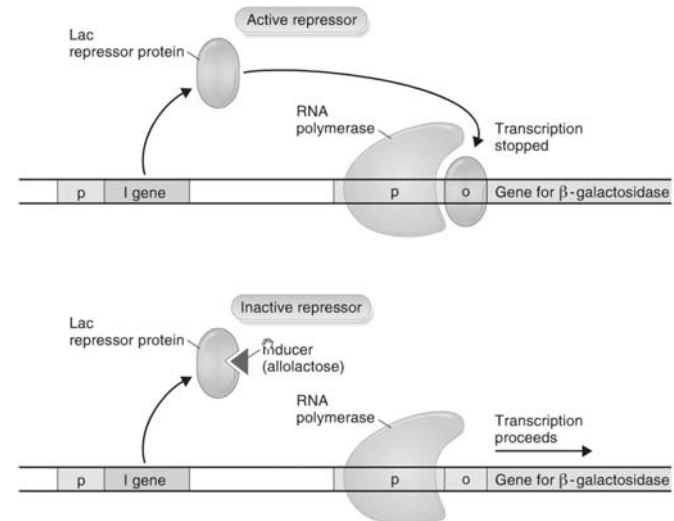
Transcription

- **RNA polymerase** - $\alpha\beta\beta'\sigma$
 - $\alpha\beta\beta'$ – core
 - σ binds to promoters
 - holoenzyme = core + σ
- inhibited by **rifampin** (binds β subunit)
- initiation - holoenzyme binds to promoter (-10, -35)
- open complex (DNA melting, transcription bubble)
- σ falls off
- termination at terminator (factor independent vs. Rho dependent)

Transcription

- **regulation** of protein synthesis is primarily at level of **initiation of transcription** involving regulatory DNA binding proteins to turn on/off genes in response to environmental conditions (remember the Lac operon)
- **polycistronic operons**, several genes transcribed from same promoter and regulated by the same conditions

Transcription Operons and Regulation

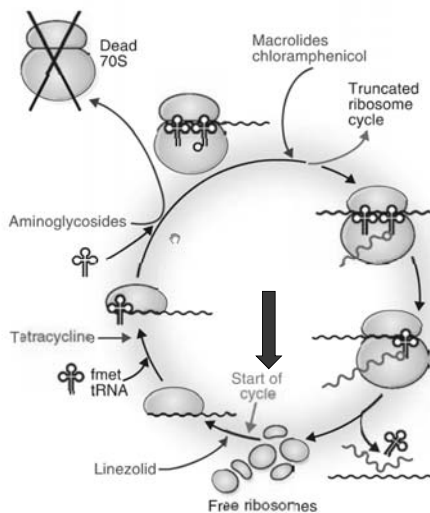


- **Quorum sensing** - regulation in bacterial communities such as biofilms
 - small **inducer molecules** are secreted
 - when concentration in environment reaches threshold (quorum has been attained), **gene expression** changes

Translation - Ribosomes

- similar but different from eukaryotic
- **70S** ribosomes composed of **50S** and **30S** subunits
- **co-transcription-translation**
- **target of many useful antimicrobials:**
 - aminoglycosides (streptomycin, kanamycin, gentamicin, neomycin)
 - tetracyclines
 - chloramphenicol
 - macrolides (erythromycin, azithromycin)

Translation - Antibiotics



- **Initiation**
 - mRNA with ribosome binding site upstream of ATG
 - Initiation Factors (IFs)
 - Small subunit
 - fMet-tRNA
 - Large subunit
- **Elongation**
 - Recognition of tRNA
 - Peptidyl transfer
 - Translocation
- **Termination**
 - Stop codons
 - TAA, TAG, TGA

Protein Localization

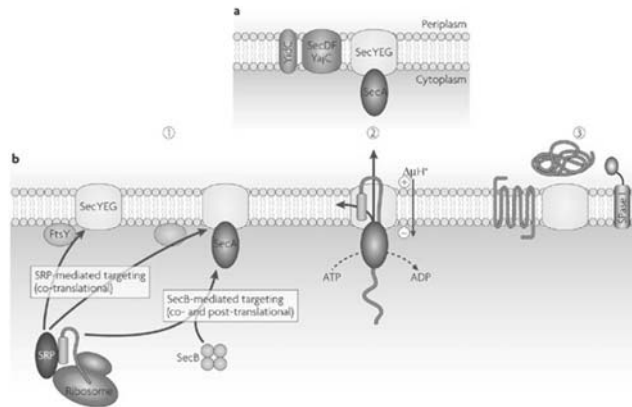
- Cytosol (Cytoplasm) – easy
- Cell membrane
- Periplasm (gram-negative)
- Outer membrane (gram-negative)
- Extracellular
- Inside host cells

Export/Secretion

Primary = **Sec pathway**

N terminal hydrophobic leader sequence

Secondary = Tat (twin arginine transport)

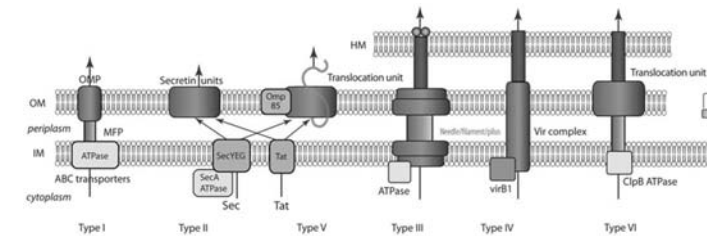


Nature Reviews | Microbiology
Nature Reviews Microbiology 5, 839-851 (November 2007)

Export/Secretion

Gram-negative beyond outer membrane

- 6 pathways
- Differ in:
 - reliance on Sec system
 - targeting extracellularly or injected into host cells



Summary of known bacterial secretion systems. HM: Host membrane; OM: outer membrane; IM: inner membrane; OMP: outer membrane protein; MFP: membrane fusion protein. ATPases and chaperones are shown in yellow. Tseng *et al. BMC Microbiology* 2009 9(Suppl 1):S2 doi:10.1186/1471-2180-9-S1-S2

Growth

- **Fast** - as little as 10 min. generation time (*Vibrio vulnificus*) as long as 24 hr. (*Mycobacterium tuberculosis*)

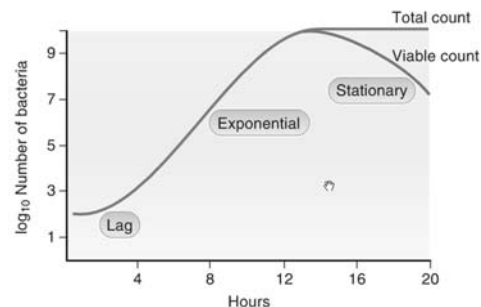
- **Phases: lag, log (exponential), stationary, death**

Calculating yield: $N_t = N_0 \times 2^g$

g = number of generations

Simple rule of thumb:
3 gen. = 10X increase

Note: You might be asked to perform some simple growth calculations on exams.



Biofilms - communities on solid/liquid environments

- change metabolism
 - **glycocalyx** holds the cells together
 - **slow** metabolism and growth.
 - resistant to antibiotics and host defenses
 - **planktonic** bacteria are free, individual – NOT in biofilm.
 - **quorum sensing**

- Contaminated devices (catheters, artificial valves, etc.)

- Body - tooth plaque, heart valves

Temperature:

- **Mesophiles** - grow best at our **body temperature - 37°C**
- **Special growth temperatures:**
 - *Campylobacter* - 42°C
 - *Listeria* and *Yersinia enterocolitica* - 4°C

Bacterial culture:

- provide all necessary things for growth
- **Fastidious** organisms require many nutrients
- **Simple** requirements can make everything from scratch
- **Some bacteria cannot be cultured in vitro**
 - *Chlamydia* and *Rickettsia* - tissue culture like viruses
 - *Treponema pallidum*, *Mycobacterium leprae* not at all, require animal infection
- Cannot predict virulence by growth (some slow or non-culturable bugs can still kill you!).

Bacterial Genetics

- **Impact on medicine**
 - **Antibiotic resistance** through mutation, plasmids, genetic exchange
 - Genetics of **virulence** (bacteriophages encoding virulence traits)
 - **Plasmids** encoding virulence traits and antibiotic resistance

The bacterial genome:

- **chromosome**
- **plasmids**
- **bacteriophage**
- **insertion sequences**
- **transposons**

haploid - one copy of chromosome, mutations are homozygous (exception – *Neisseria*)

Mutation

- **change in the DNA sequence**
- 10^{-9} /base or 10^{-6} /gene per replication
- happen all of the time, regardless of growth conditions - are they selected for to become enriched in the bacterial population?
- **point mutations** - single bases (insertion, deletion, missense, nonsense)
- **macro-mutation** - affect >1 base (insertion, deletion, inversion, duplication)

- can change a gene so that protein is no longer affected by an antibiotic, yet still retains its function
- effects of genotype on phenotype
 - silent
 - loss of function
 - altered function
 - completely new genes are not constructed by a single mutation

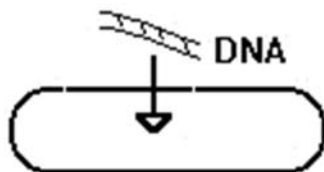
Genetic exchange

- **Importance**
 - moving **antibiotic resistance** genes among bacteria
 - moving **virulence** gene among bacteria
 - changing the **antigenic make-up** to avoid immunity
- **Mechanisms**
 - **transformation** - uptake of naked DNA
 - **transduction** - bacteriophage as vectors
 - **conjugation** - plasmids moved by cell-cell contact

Transformation

- recipient cell must be **competent for uptake of DNA**
- **natural competence** versus **artificial competence**
- only **certain bacteria** are naturally transformable - *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Vibrio*

TRANSFORMATION

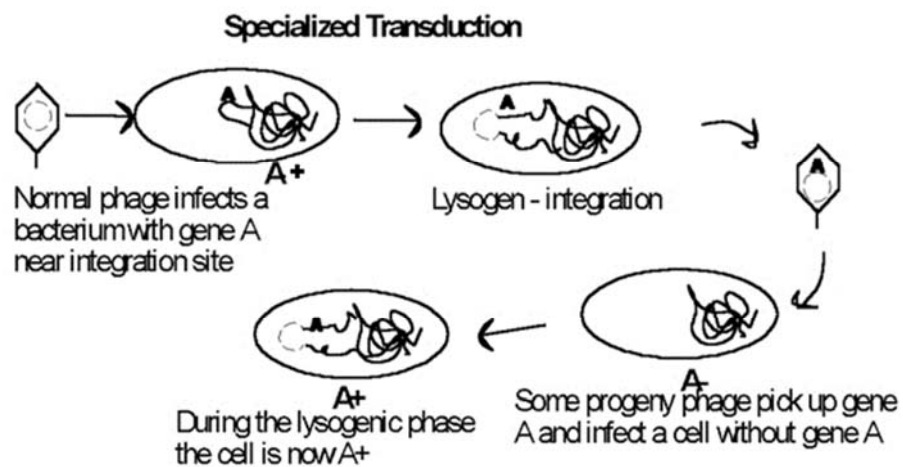
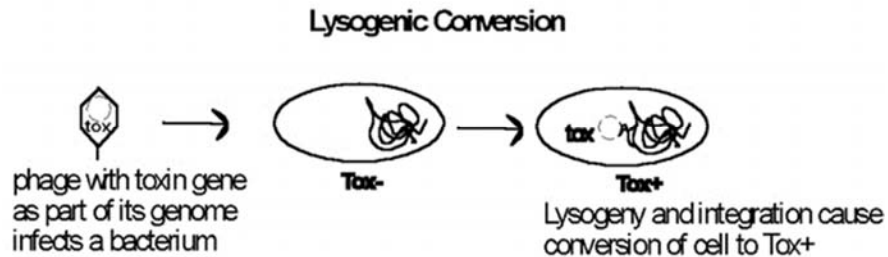


Transduction

- **bacteriophage (phage)** are viruses of bacteria
 - **lytic** - always lyse (kill) host bacterial cell
 - **temperate** - can stably infect and coexist within bacterial cell (**lysogeny**) until a **lytic phase** is induced
- **lysogeny**
 - phage genome = **prophage**
 - bacterial cell = **lysogen**
 - **lysogenic conversion**
 - **phage encodes observable function**
 - (e.g., diphtheria toxin in *Corynebacterium diphtheriae*)

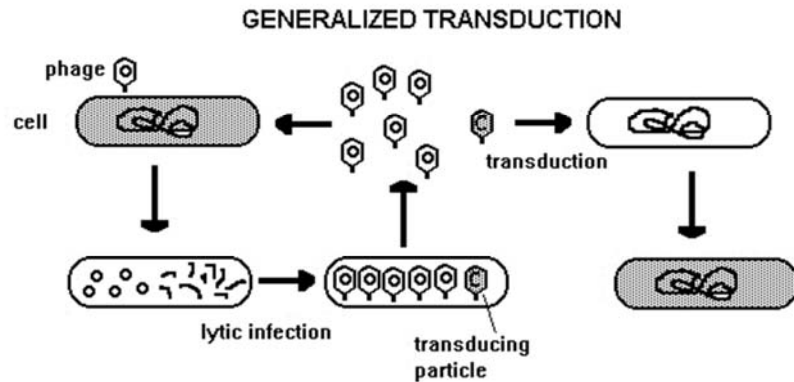
Specialized transduction

- Some prophages **integrate** into the bacterial genome at a specific location.
- When a prophage is induced to **lytic phase**, it may drag along a piece of the **bacterial genome next to the integration site** and move that bacterial sequence into the new recipient host cell, **changing the recipient's genome**.
- Not very important medically since only selected genes can be transferred.



Generalized transduction

- When a phage lyses the host bacterial cell, it normally **packages phage genome** into the capsid.
- Sometimes the capsid is **accidentally** filled with random pieces of **bacterial genome**, possibly including plasmids.
- When the capsid injects the host genes into a new recipient, the new gene can **recombine** into the recipient genome and cause a change.
- **Virulence and antibiotic resistance genes** can be moved by generalized transduction.



NOTE:

- **lysogeny**
 - **phage gene** = lysogenic conversion
 - **host gene** = specialized transduction.
- **generalized transduction**
 - phage particle = **vehicle** to move **bacterial genes** from one cell to another
 - phage genome is not moved

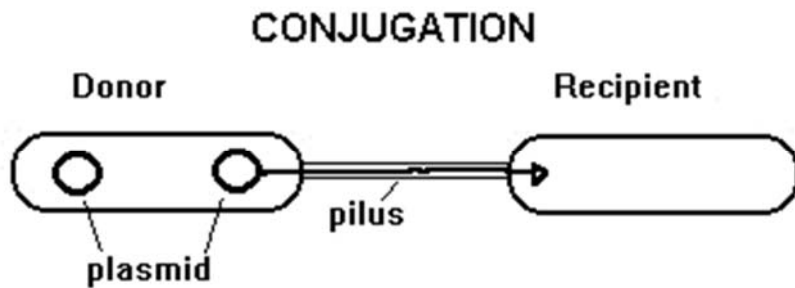
Conjugation

Plasmids - Non-chromosomal DNA

- **usually circular**
- **can be transmissible between cells by genetic exchange (conjugation)**
- **some encode virulence properties, antibiotic resistance**

Conjugation

- 3 possible states for conjugation
 - **conjugative** - plasmid encodes all of the functions for conjugation and can move itself from the donor cell to the recipient cell
 - **mobilizable** - plasmid cannot move itself, but can be moved with help from a conjugative plasmid
 - **non-transmissible** - can't move by conjugation
- **conjugation functions**
 - synthesis of sex **pilus**
 - **cell to cell contact** via pilus
 - **copying plasmid DNA and transfer** of copy into recipient cell



- **bacteria containing a conjugative plasmid are called donor, male, (F+)**
- **bacteria receiving the plasmid are called recipient, female, (F-)**
- F plasmid is a specific *E. coli* plasmid that has nothing to do with medicine other than its historical and laboratory use (and standardized exams)

- other terms of interest

- **Hfr** - a plasmid integrates into the chromosome, conjugation will move part of the chromosome into the recipient (not of medical relevance)
- **F'** - plasmid integrates into the chromosome, excision drags along piece of the chromosome. F' can move host DNA between cells (not of medical relevance) (similar to specialized transduction)

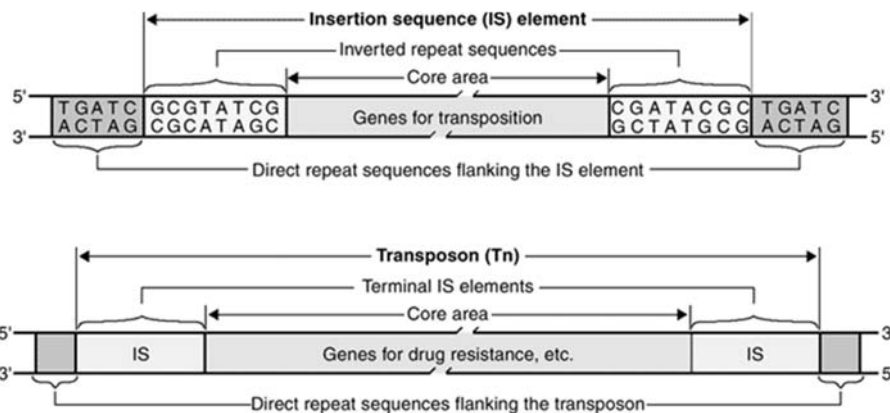
- Unlike transduction by phages, **most plasmids are more promiscuous in their host range.**
- importance of conjugation - **moving plasmids encoding multiple antibiotic resistance genes (R plasmids)** among diverse bacterial

Other mobile DNA elements

- **Insertion Sequences and Transposons**
- Part of other genetic elements - chromosome, plasmid. They move from one site in DNA to another **WITHIN the same cell (transposition)**

Insertion sequence (IS)

- gene encoding transposition enzyme (**transposase**) flanked by **inverted repeats** of DNA sequence
- can interrupt genes if they insert into them

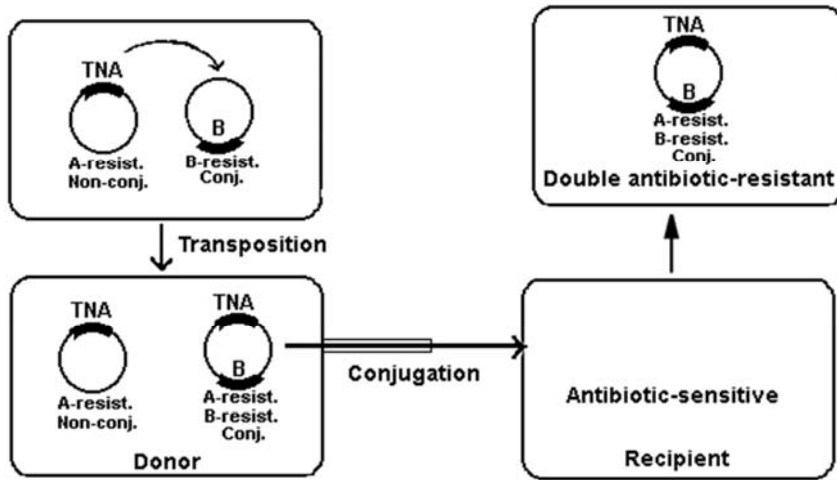


Transposon (Tn)

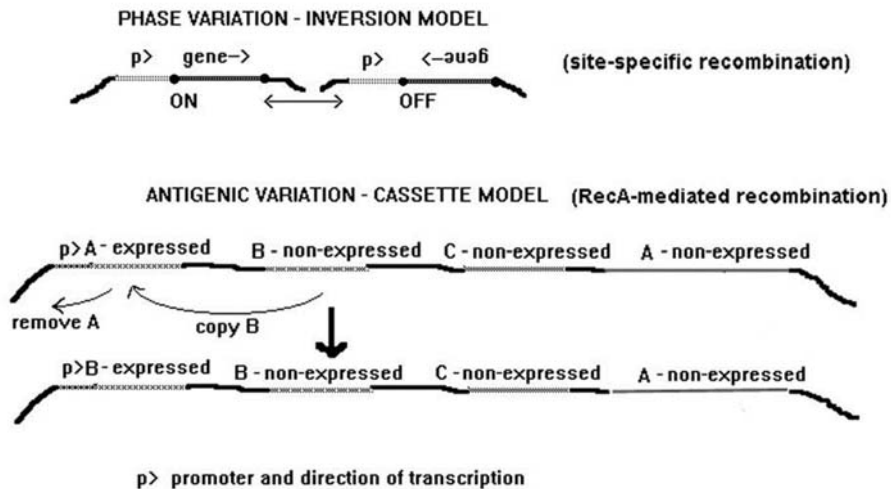
- composite insertion sequence
- gene usually encoding an observable function (e.g., **antibiotic resistance**) flanked by two copies of an insertion sequence
- insertion sequences = transposition engine
- move genes between chromosome and plasmids or between different plasmids
- **medical importance - antibiotic resistance genes** in transposons in antibiotic resistance plasmids

Phase variation and Antigenic variation

- **Phase variation**
 - change in DNA sequence leading to an **ON-OFF switch** of a gene or **A-B switch** of two different genes
 - caused by inversion of a DNA sequence
- **Antigenic variation**
 - change in DNA sequence leading to switch of expression among **multiple possible genes**
 - most common mechanism is the **cassette model**
 - non-expressed copies (**silent**) of a gene (the cassettes) are copied or recombined into a site where the cassettes can be **expressed**



Regulation of Gene Expression

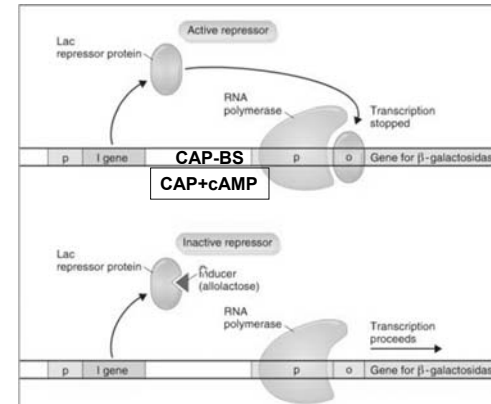


Regulation of gene expression

General information

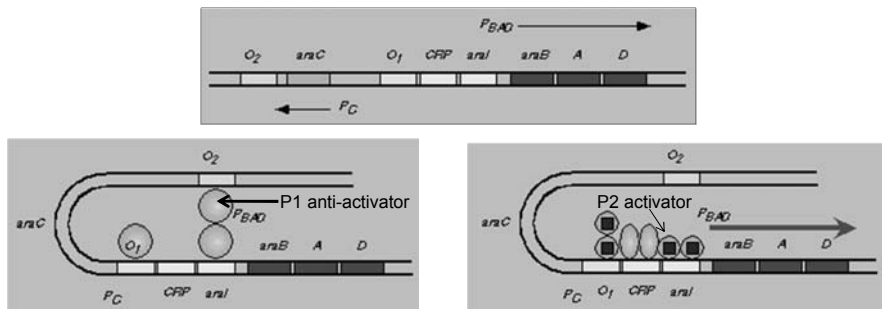
- A. orderly and controlled expression
 - growth phase, nutritional and stress conditions, environment vs. in host
- B. most regulation at initiation of transcription; however, some post-transcriptional
 - mRNA stability, translational regulation, post-translational
- C. operon - region of DNA (genes and required cis-active sites) expressed from same promoter therefore on same mRNA
- D. negative regulation - when active regulator turns off expression
- E. positive regulation - when active regulator turns on expression
- F. regulators - repressor - turn off binding to operators; activators - turn on binding to activator sites
- G. effector molecules - inducer - binds to repressor or activator to turn on expression corepressor - binds to repressor turning off expression
- H. constitutive mutant - always on - more difficult for positive regulation than repression
- I. cistron - operon - regulon - stimulon

lac operon - repression, utilization



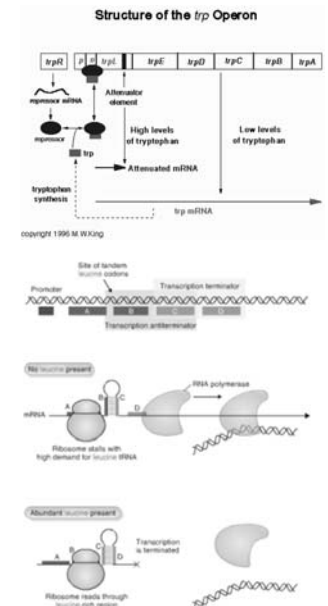
- A. LacI repressor binds to operator in absence of inducer (allo-lactose, lactose, IPTG) - prevents initiation of transcription
- B. lacUV5 promoter - not sensitive to catabolite repression
- C. trp-lac -tac stronger; trc even stronger
- D. catabolite repression - CAP+cAMP required for full expression
- E. what are effects of mutations in different elements - constitutive, dominant off, dominant on

Arabinose operon - activation - utilization



- A. araC araO2..pC araO1..CAP (CRP) araI pBAD BAD
- B. AraC: P1 anti-activator - ara; P2 activator + ara
- C. AraC P2 binds to araI activating pBAD
- D. AraC P1 binds to araO2 and araI forming bend
- E. AraC represses its own synthesis in the absence of ara (like LacI) at araO2 and araA to loop out pC
- F. catabolite repression also

trp (leu) operon - biosynthesis



- A. biosynthesis of Trp
- B. repressor and aporepressor
- C. ptrp trpL trpE.... ..trpR
- D. TrpR only binds to and represses ptrp in the presence of Trp
- E. attenuation
 1. trpL gene (leader)
 2. 2 Trp codons - ribosome stalls w/o trp, enables B:C pairing, no C:D
 3. +Trp - rib moves to stop codon, preventing B:C, enabling C:D, which is a factor-independent terminator

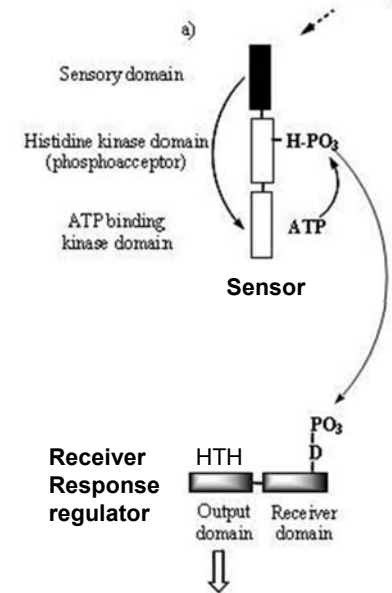
An Example of Global Regulation

Catabolite repression - CAP regulon

- misnomer, since the CAP protein is an activator
- catabolite-sensitive operons
- cAMP made by adenylate cyclase (*cya* gene) - ATP → cAMP
- decrease energy level - increased cAMP
- CAP/CRP (*crp* gene) is usually an activator, but can also be a repressor
- CRP-cAMP is the active form that binds specific DNA sequence
- CRP-cAMP has affinity for RNA-Pol (α subunits)
- CRP regulon genes have poor upstream elements that usually decrease RNA-Pol binding (weak)
- CRP-regulated genes usually are regulated by other regulators, so at least 2 levels of regulation needed (web of regulation)

Two Component Regulatory Systems

- A common method for sensing signals and transmitting the signal to change transcription.
- Usually 2 proteins
 - Sensor (S) - His kinase
 - Receiver (R) - Transcriptional regulator, activity is changed upon phosphorylation
- Both domains/functions can be combined into a single protein
- Sensors often span cell membrane

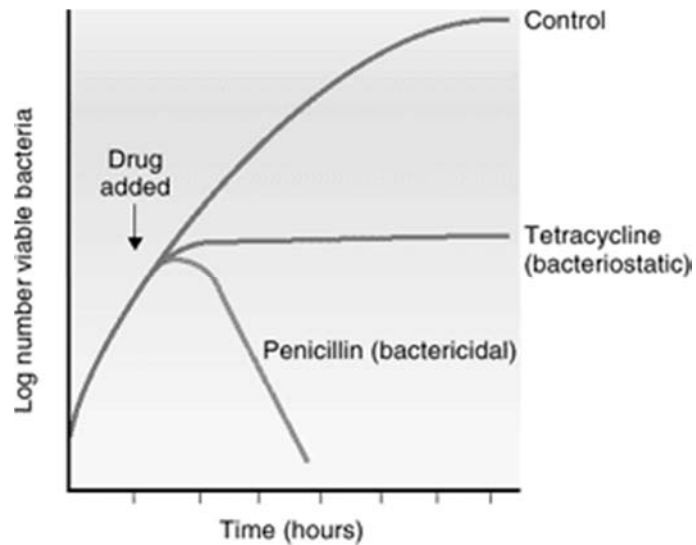


Antimicrobial chemotherapy

- **Selective toxicity**
 - **toxic to bacteria, not bad for us**
 - Selective toxicity based on **differences in physiology** between bacteria and us
 - **therapeutic index** = $\frac{\text{toxic dose to us}}{\text{therapeutic dose against bugs}}$ (high is good)
- **allergenicity**

Bactericidal vs. bacteriostatic

- **bactericidal - kills bacteria (irreversible)**
- **bacteriostatic - stops growth (reversible)**
- measured in lab as:
 - **Minimum Bactericidal Concentration (MBC)**
 - lowest dose for complete killing
 - **Minimum Inhibitory Concentration (MIC)**
 - lowest dose for stasis



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Pharmacologic absorption and distribution in body

- oral vs. i.v.
- penetration to relevant site (e.g., blood brain barrier or inside of host cells)
- rate of excretion
- rate of metabolism

Broad spectrum vs. narrow spectrum

- broad good for unknown bacterial agent with serious effects
- narrow good for known bacterial agent

Summary of key antimicrobials

- **peptidoglycan**
 - β -lactams
 - **inhibit transpeptidation (D-Ala-D-Ala)**
 - **penicillins** (methicillin, amoxicillin)
 - **cephalosporins** (in third generation)

peptidoglycan - continued

- **vancomycin** inhibits transpeptidation and transport (recognizes D-Ala-D-Ala, note difference with β -lactams)
- **bacitracin** transport of the subunits across membrane
- vancomycin and bacitracin are too big to fit through porins of gram-negative bacteria

Membranes

- gram-negatives - **outer membrane** - polymyxins (similar to cationic detergents)
- gram-positives – daptomycin – create K⁺ channels

Protein synthesis - ribosome

- **aminoglycosides**: gentamicin, kanamycin, neomycin, streptomycin
- **aminocyclitols**: spectinomycin
- **tetracyclines**
- **chloramphenicol**
- **macrolides**: erythromycin, azithromycin
- **clindamycin**: similar to macrolides
- **streptogramins** - similar to macrolides
- **oxazolidinones** (linezolid/ketolids)- synthetic, similar to macrolides, inhibits initiation of translation in gram-positives (Zyvox)
- **inhibit tRNA synthesis** (isoleucine) - **mupirocin**, topical

DNA synthesis

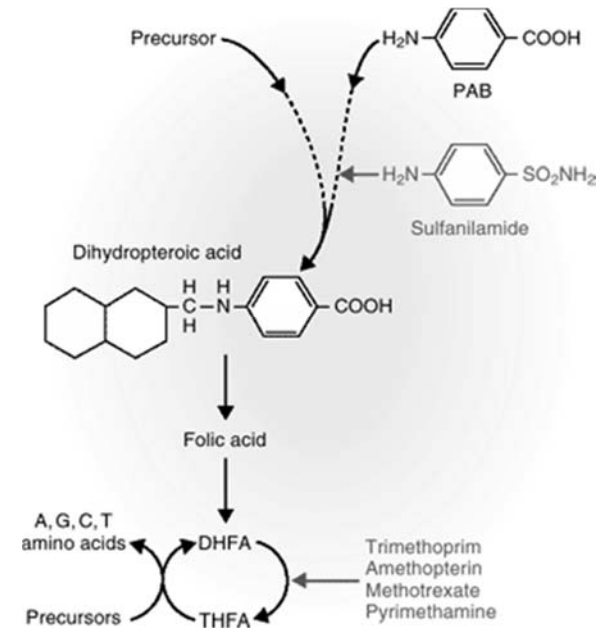
- **quinolones** inhibit gyrase (supercoiling)
 - **nalidixic acid, ciprofloxacin**
- **metronidazole** disrupts DNA after reduction in
 - anaerobes (and some protozoans)

RNA synthesis

- **rifampin** (rifampicin, rifamycin)

Metabolic inhibitors - folic acid inhibitors

- **sulfonamides** - PABA analogs block dihydropteroate synthetase (we don't have this)
- **trimethoprim** blocks dihydrofolate reductase (ours is less sensitive)
- **dapsone** (acid fast)



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