Dissemination of Antibiotic Resistance Genomes

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Life in an infectious disease-free environment
Antibiotics/vaccines

Next 2 sessions on this major clinical and genetic problem

1) Describe how bacterial cells organize, mutate, and reorganize the genes that encode the ability to resist the action of antibiotics.

2) Explore mechanisms by which those bacterial cells can and do exchange those resistance genes.

Extra figures
* = to be discussed in detail later

GENOMIC ORGANIZATION
Introduction to genomes
Bacterial genomes
Plasmid genomes
Viral genomes

TRANSPOSITION
The Basics
Types of Transposable Elements
R plasmids and Multiple Resistance
All genomes are made of DNA with the exception of some viruses (RNA).

Genomes range in size $10^4$ bp (small viruses) to $10^{12}$ bp (amoeba).

Humans have a complex genome.

Some bacteria have a simple genome.
But, some bacteria have a complex genome

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<tr>
<th>Region</th>
<th>Geometry</th>
<th>Size (bp)</th>
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9 circular plasmids

Borrelia (Lyme disease)

13 linear plasmids

GENOMIC ORGANIZATION

• Chromosomal (Bacterial) Genome
• Plasmid (Episome) Genome
• Bacterial Virus (Phage) Genome

CHROMOSOMAL GENOME

large (megabases - average 4000 genes)
double-stranded DNA
tightly packed structure (nucleoid)
Typically, but not always, haploid
circular or linear

CLINICAL RELEVANCE

can encode for certain
antibiotic resistance & virulence factors
usually within pathogenicity islands
Structure of Bacterial chromosome
The traditional view
*A tangled knot of DNA*

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Exponential growth tran active
Late stationary phase
Lag phase tran inactive
Early stationary phase

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Adapted from Kim et al., 2004

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Beads-on-a-string chromatin
30-nm chromatin fiber of packed nucleosomes
1400 nm (transcriptionally inactive)
PLASMID GENOME
(episome)
autonomous, self-replicating,
extrachromosomal, double-stranded DNA
tend to be small (kilobases)
usually circular, but can be linear

CLINICAL RELEVANCE
genes for antibiotic resistance (R plasmids*)
genes for virulence factors
easily transferred from host to host

1. CONJUGATIVE PLASMIDS*
autonomous transfer from host to host
within or between species

CLINICAL RELEVANCE
major cause of spread
of multiple antibiotic resistances

2. NON-CONJUGATIVE PLASMIDS
cannot transfer themselves,
BUT can be transferred by conjugative plasmids
often used for genetic engineering

BACTERIAL VIRUS GENOME
(Bacteriophage, phage)

RNA or DNA
double- or single-stranded
linear or circular
3 to 300 kilobases

CLINICAL RELEVANCE
can carry virulence factors
e.g., Diptheria Beta-toxin
Cholera toxin*
**BACTERIOPHAGE LIFESTYLE CHOICES**

<table>
<thead>
<tr>
<th>Lytic Infection*</th>
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<tr>
<td>phage replicates itself</td>
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<tr>
<td>lyses the host cell</td>
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<tr>
<td>releases progeny phage</td>
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<table>
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<tr>
<th>Lysogenic Infection*</th>
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<tbody>
<tr>
<td>phage becomes latent</td>
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<tr>
<td>does not replicate</td>
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<tr>
<td>circularize or integrate into the host chromosome</td>
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<tr>
<td>latent genome called prophage</td>
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**GENOMIC ORGANIZATION**

**TRANSPOSITION**

Transposable elements
mediate self-transposition
jump from genome to genome

**CLINICAL RELEVANCE**

major carrier of antibiotic resistance genes
evolution of R plasmids
TRANSPOSABLE ELEMENTS

i) insertion sequence (IS) elements
   ii) transposons (Tn)

INSERTION SEQUENCE (IS) ELEMENTS

~ 1000 bases

carry only genes or sequences for transposition
recombinase (transposase) = transposition enzyme
inverted repeats = recombinase recognition sites

insertion into a gene causes mutation

INSERTION SEQUENCE ELEMENT

Genes for Transposition only

AGTCATGCAAT TAGTACGTGA ~ 1000 bp ATTCGATCGACT TAAACCCTCTGA

Inverted Repeats
TRANSPOSONS
transposable element that carries genes for
i) transposition
ii) other functions

antibiotic resistance = transposon
genes for conjugation = conjugal transposon
bacteriophage = transposable phage
TRANSPOSABLE BACTERIOPHAGE

Gene Exchange Systems*

CAN MOVE TRANSPOSONS BETWEEN CELLS
permits transfer of resistance
from cell-to-cell
within species
from one species to another

TRANSPOSABLE BACTERIOPHAGE

phage genome between two IS elements

phage can alternate
between lytic and lysogenic states

when lysogenic
phage can transpose
i.e., jump from phage genome
to chromosome or plasmid
CONJUGAL TRANSPOSON

transfer machinery for conjugation between two IS elements

found in Streptococcal Enterococcus faecalis & many Bacteroides species

CONJUGAL TRANSPOSON

Conjugal transposons like all transposons must be located within a genome of some kind

R PLASMIDS*
carry multiple antibiotic resistance genes

resistance genes often encode enzymes that
i) inactivate antibiotics or
ii) reduce permeability to antibiotics
many Gram-negative bacteria carry R plasmids that carry multiple resistances
thus, selection for one antibiotic can cause selection for multiple antibiotic resistance
can transfer between species nonpathogenic bacteria that carry R plasmid often act as reservoir to pathogenic bacteria
Selection for Km also selects for Cm