

Implications of Gene Transfer and Inducible Resistance for Successful Therapy

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Why is horizontal gene transfer so important?

- **Resistance acquired by mutation**

- Usually need multiple mutations in essential bacterial genes
- One step mutations can make bacteria less fit, need compensating mutations

(R. Lenski, Ciba Found. Symp. 1997. 207:131-140)

- Many random mutations will be deleterious

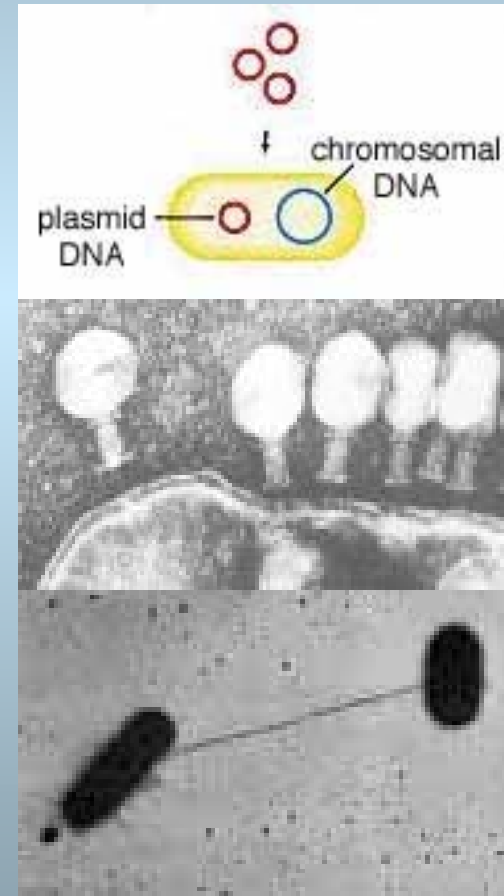


Why is horizontal gene transfer so important?

- **Resistance acquired by horizontal transfer**
 - New gene unlikely to be deleterious
 - Promoter mutations can lead to expression

Types of horizontal gene transfer events

- **Narrow host range - between closely related bacteria**
 - Transformation
 - Phage transduction
- **Broad host range - cross species and genus lines**
 - Conjugation - can occur within an hour



Conjugal gene transfer elements

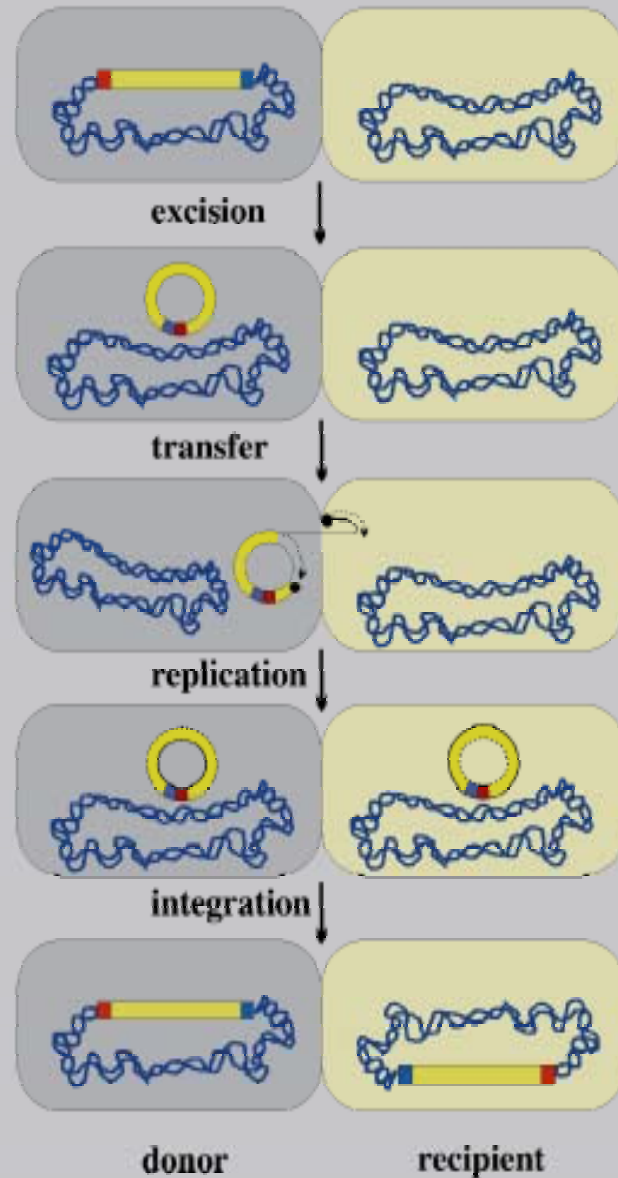
- **Plasmids**

- Can acquire new resistance genes
 - Transposons
 - Integrons
- Bacteria acquire compensating mutations that lead to greater fitness

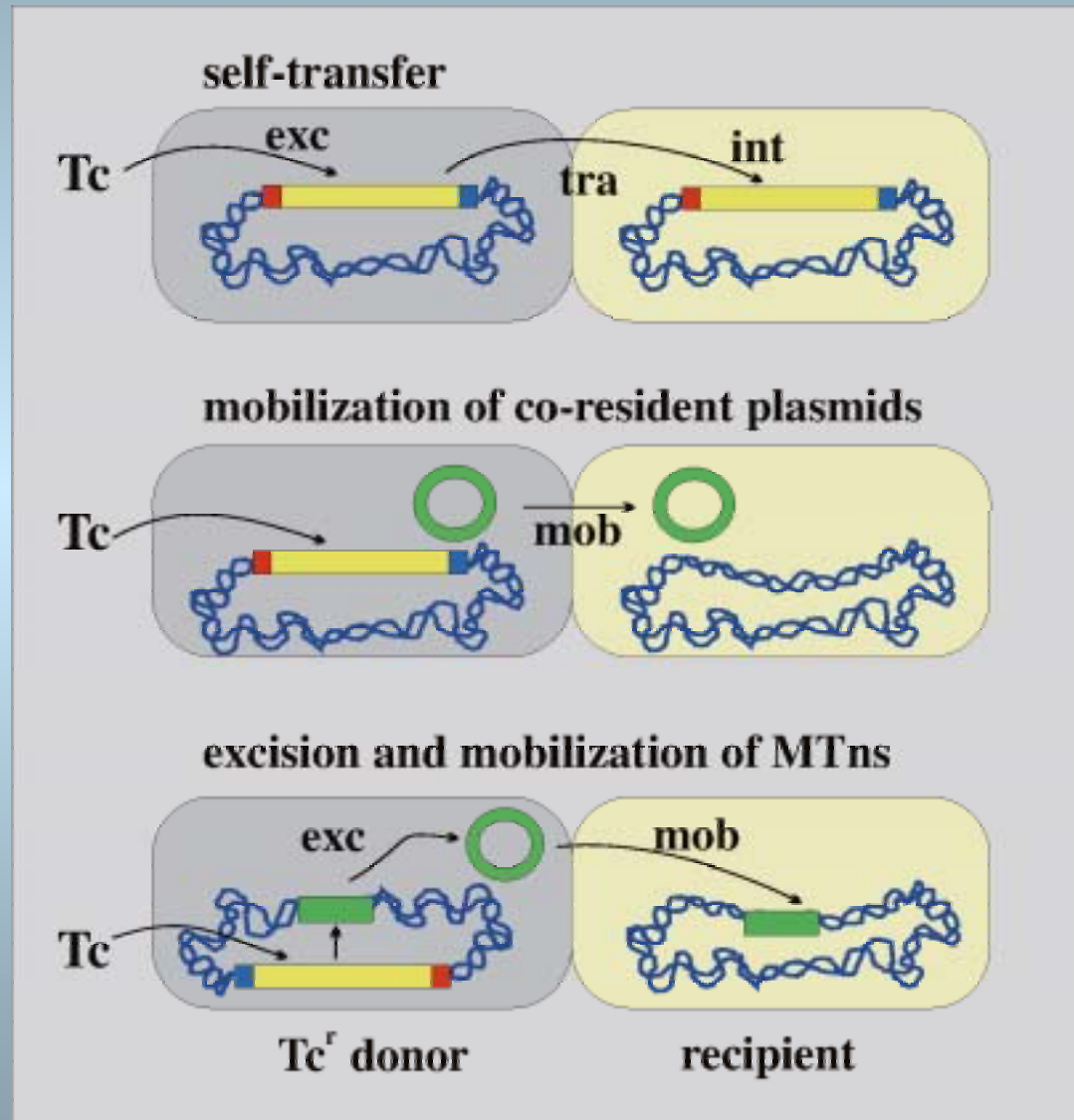
- **Conjugative transposons**

- Can be as promiscuous as plasmids
- Stably integrated into the genome - not easily lost

Steps involved in the intercellular transfer of a CTn



Transfer potential of *Bacteroides* CTns



Stability of plasmids and conjugative transposons

- **Naturally occurring plasmids**
 - Usually have a low copy number - enhances stability
 - Often encode plasmid maintenance systems
- **Conjugative transposons**
 - Integrated in the chromosome

Stability of plasmids and conjugative transposons

- **Inducible resistance genes and inducible transfer decrease fitness toll**
 - Cessation of antibiotic treatment or changing antibiotics may not cause resistant strains to disappear
 - Even when incidence of resistance decreases, a “hard core” of strains persist

Can resistance be prevented?

- **End abuse and overuse of antibiotics**
- **Treating a patient with antibiotics means treating the patient's microflora**
 - Can members of the microflora serve as reservoirs of resistance genes?



Antibiotic resistance gene distribution in Community and Hospital Isolates of *Bacteroides* spp.

Source of Isolates	No.	Percentage of Isolates Carrying					
		<i>tetQ</i>	<i>ermF</i>	<i>ermG</i>	<i>cfxA</i>	CTn	NBU
Community (pre-1970)	69	32	0	0	0	42	51
Clinical (pre-1970)	23	22	9	0	4	30	35
Community (1996-1997)	102	81	15	8	3	84	74
Clinical (1980-1995)	87	86	30	18	14	85	84

Horizontal Gene Transfer

Bacillus spp.

ermG

Bacteroides spp.

Enterococcus spp.
Staphylococcus spp.
Streptococcus spp.

ermB

Bacteroides spp.

Enterococcus spp.
Staphylococcus spp.
Streptococcus spp.
Actinomyces spp.
Bifidobacterium spp.

tetM

Campylobacter spp.
Fusobacterium nucleatum
Gardenella vaginalis
Haemophilus spp.
Neisseria spp.
Veillonella spp.

?

ermF
tetQ

Bacteroides spp.

Summary

